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#### (57) Abstract

The present invention provides human proteins having hydrophobic domains, DNAs encoding these proteins, and expression vectors for these DNAs as well as eukaryotic cells expressing these DNAs.

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#### DESCRIPTION

# Human Proteins Having Hydrophobic Domains and DNAs Encoding These Proteins

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#### TECHNICAL FIELD

The present invention relates to human proteins having hydrophobic domains, DNAs encoding these proteins, expression vectors for these DNAs as well as eukaryotic cells expressing these DNAs. The proteins of the present invention can be employed as pharmaceuticals or as antigens for preparing antibodies against these proteins. The human cDNAs of the present invention can be utilized as probes for genetic diagnosis and gene sources for gene therapy. Furthermore, the cDNAs can be utilized as gene sources for large-scale production of the proteins encoded by these cDNAs. Cells into which these genes are introduced to express secretory proteins or membrane proteins in large quantity can be utilized for detection of the corresponding receptors or ligands, screening of novel small molecule pharmaceuticals and the like.

#### BACKGROUND ART

Cells secrete many proteins extracellularly. These secretory proteins play important roles in the proliferation control, the differentiation induction, the material transport, the biophylaxis, and the like of the cells. Unlike intracellular proteins, the secretory proteins exert their actions outside the cells. Therefore, they can be administered in the intracorporeal manner such as the injection or the drip, so that they possess hidden

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potentialities as pharmaceuticals. In fact, a number of human secretory proteins such as interferons, interleukins, erythropoietin, thrombolytic agents and the like have been currently employed as pharmaceuticals. In addition, secretory proteins other than those described above are undergoing clinical trials for developing their use pharmaceuticals. It is believed that the human cells produce many unknown secretory proteins. Availability of these secretory proteins as well as genes encoding them expected to lead to development of novel pharmaceuticals utilizing these proteins.

On the other hand, membrane proteins play important roles, as signal receptors, ion channels, transporters and like in the material transport and the transduction through the cell membrane. Examples thereof include receptors for various cytokines, ion channels for the sodium ion, the potassium ion, the chloride ion and the like, transporters for saccharides and amino acids and the like. The genes for many of them have already been cloned. It has been clarified that abnormalities of these membrane proteins are involved in a number of previously cryptogenic diseases. Therefore, discovery of a new membrane protein is expected to lead to elucidation of the causes of many so that isolation of new genes encoding the membrane proteins has been desired.

Heretofore, due to difficulty in the purification from human cells, many of these secretory proteins and membrane proteins have been isolated by genetic approaches. A general method is the so-called expression cloning method, in which a cDNA library is introduced into eukaryotic cells to express cDNAs, and the cells secreting, or expressing on the surface of membrane, the protein having the activity of

interest are then screened. However, only genes for proteins with known functions can be cloned by using this method.

In general, a secretory protein or a membrane protein possesses at least one hydrophobic domain within the protein. After synthesis in the ribosome, such domain works as a secretory signal or remains in the phospholipid membrane to be entrapped in the membrane. Accordingly, if the existence of a highly hydrophobic domain is observed in the amino acid sequence of a protein encoded by a cDNA when the whole base sequence of the full-length cDNA is determined, it is considered that the cDNA encodes a secretory protein or a membrane protein.

#### OBJECTS OF THE INVENTION

The main object of the present invention is to provide novel human proteins having hydrophobic domains, DNAs encoding these proteins, and expression vectors for these DNAs as well as transformed eukaryotic cells that are capable of expressing these DNAs. This object as well as other objects and advantages of the present invention will become apparent to those skilled in the art from the following description with reference to the accompanying drawings.

## 25 BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02539.

Fig. 2 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02770.

Fig. 3 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02869.

Fig. 4 illustrates the hydrophobicity/hydrophilicity

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profile of the protein encoded by clone HP02956.

- Fig. 5 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02962.
- Fig. 6 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03014.
- Fig. 7 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10608.
- Fig. 8 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10609.
- 10 Fig. 9 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10611.
  - Fig. 10 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10617.
  - Fig. 11 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02837.
    - Fig. 12 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02991.
  - Fig. 13 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03063.
  - Fig. 14 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03091.
    - Fig. 15 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03092.
  - Fig. 16 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03116.
    - Fig. 17 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10618.
    - Fig. 18 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10619.
- Fig. 19 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10622.
  - Fig. 20 illustrates the hydrophobicity/hydrophilicity

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profile of the protein encoded by clone HP10625.

Fig. 21 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02883.

Fig. 22 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03140.

Fig. 23 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10628.

Fig. 24 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10629.

Fig. 25 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10635.

Fig. 26 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10636.

Fig. 27 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10640.

Fig. 28 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10644.

Fig. 29 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10656.

Fig. 30 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10672.

Fig. 31 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03194.

Fig. 32 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03219.

Fig. 33 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03236.

Fig. 34 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03237.

Fig. 35 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03267.

Fig. 36 illustrates the hydrophobicity/hydrophilicity

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profile of the protein encoded by clone HP03270.

Fig. 37 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03298.

Fig. 38 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10631.

Fig. 39 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10658.

Fig. 40 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10663.

Fig. 41 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03165.

Fig. 42 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03266.

Fig. 43 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03287.

Fig. 44 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10665.

Fig. 45 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10669.

Fig. 46 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10670.

Fig. 47 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10671.

Fig. 48 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10673.

Fig. 49 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10675.

Fig. 50 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10683.

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# SUMMARY OF THE INVENTION

As the result of intensive studies, the present inventors have successfully cloned cDNAs encoding proteins having hydrophobic domains from the human full-length cDNA bank, thereby completing the present invention. Thus, the provides a human protein invention present hydrophobic domain(s), namely a protein comprising any one of an amino acid sequence selected from the group consisting of SEQ ID NOS: 1 to 10, 31 to 40, 61 to 70, 91 to 100, and 121 to 130. Moreover, the present invention provides a DNA encoding the above-mentioned protein, exemplified by a cDNA comprising any one of a base sequence selected from the group consisting of SEQ ID NOS: 11 to 30, 41 to 60, 71 to 90, 101 to 120 and 131 to 150 as well as an expression vector that is capable of expressing such DNA by in vitro translation or in eukaryotic cells and a transformed eukaryotic cell that is capable of expressing such DNA and of producing the above-mentioned protein.

## 20 DETAILED DESCRIPTION OF THE INVENTION

The proteins of the present invention can be obtained, for example, by a method for isolating proteins from human organs, cell lines or the like, a method for preparing peptides by the chemical synthesis based on the amino acid sequence of the present invention, or a method for producing proteins by the recombinant DNA technology using the DNAs encoding the hydrophobic domains of the present invention. Among these, the method for producing proteins by the recombinant DNA technology is preferably employed. For example, the proteins can be expressed in vitro by preparing an RNA by in vitro transcription from a vector having the

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cDNA of the present invention, and then carrying out in vitro translation using this RNA as a template. Alternatively, introduction of the translated region into a suitable expression vector by the method known in the art may lead to expression of a large amount of the encoded protein in prokaryotic cells such as Escherichia coli, Bacillus subtilis, etc., and eukaryotic cells such as yeasts, insect cells, mammalian cells, etc.

In the case where the protein of the present invention is produced by expressing the DNA by in vitro translation, the protein of the present invention can be produced in vitro by introducing the translated region of this cDNA into a vector having an RNA polymerase promoter, and then adding the vector to an in vitro translation system such as a rabbit reticulocyte lysate or a wheat germ extract, which contains an RNA polymerase corresponding to the promoter. The RNA polymerase promoters are exemplified by T7, T3, SP6 and the like. The vectors containing these RNA polymerase promoters are exemplified by pKA1, pCDM8, pT3/T7 18, pT7/3 19, pBluescript II and the like. Furthermore, the protein of the present invention can be expressed in the secreted form or the form incorporated in the microsome membrane when a canine pancreas microsome or the like is added to the reaction system.

In the case where the protein of the present invention is produced by expressing the DNA in a microorganism such as Escherichia coli etc., a recombinant expression vector in which the translated region of the cDNA of the present invention is introduced into an expression vector having an origin which is capable of replicating in the microorganism, a promoter, a ribosome-binding site, a cDNA-cloning site, a terminator and the like is constructed. After transformation

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of the host cells with this expression vector, the resulting transformant is grown, whereby the protein encoded by the cDNA can be produced in large quantity in the microorganism. In this case, a protein fragment containing any translated region can be obtained by adding an initiation codon and a termination codon in front of and behind the selected translated region to express the protein. Alternatively, the protein can be expressed as a fusion protein with another protein. Only the portion of the protein encoded by the cDNA can be obtained by cleaving this fusion protein with a suitable protease. The expression vectors for Escherichia coli are exemplified by the pUC series, pBluescript II, the pET expression system, the pGEX expression system and the like.

In the case where the protein of the present invention is produced by expressing the DNA in eukaryotic cells, the protein of the present invention can be produced as a secretory protein, or as a membrane protein on the cellmembrane surface, by introducing the translated region of the cDNA into an expression vector for eukaryotic cells that has a promoter, a splicing region, a poly(A) addition site and the like, and then introducing the vector into the eukaryotic cells. The expression vectors are exemplified by pKA1, pED6dpc2, pCDM8, pSVK3, pMSG, pSVL, pBK-CMV, pBK-RSV, EBV vectors, pRS, pYES2 and the like. Examples of eukaryotic cells to be used in general include mammalian cultured cells such as monkey kidney COS7 cells, Chinese hamster ovary CHO cells and the like, budding yeasts, fission yeasts, silkworm cells, Xenopus oocytes and the like. Any eukaryotic cells may be used as long as they are capable of expressing the proteins of the present invention. The expression vector can be introduced into the eukaryotic cells by using a method known in the art such as the electroporation method, the calcium phosphate method, the liposome method, the DEAE-dextran method and the like.

After the protein of the present invention is expressed in prokaryotic cells or eukaryotic cells, the protein of interest can be isolated from the culture and purified by a combination of separation procedures known in the art. Examples of the separation procedures include treatment with a denaturing agent such as urea or a detergent, sonication, enzymatic digestion, salting-out or solvent precipitation, dialysis, centrifugation, ultrafiltration, gel filtration, SDS-PAGE, isoelectric focusing, ion-exchange chromatography, hydrophobic chromatography, affinity chromatography, reverse phase chromatography and the like.

The proteins of the present invention also include peptide fragments (of 5 amino acid residues or more) containing any partial amino acid sequences in the amino acid sequences represented by SEQ ID NOS: 1 to 10, 31 to 40, 61 to 70, 91 to 100, and 121 to 130. These peptide fragments can be utilized as antigens for preparation of antibodies. Among the proteins of the present invention, those having the signal sequences are secreted in the form of mature proteins after the signal sequences are removed. Therefore, these mature proteins shall come within the scope of the protein of the present invention. The N-terminal amino acid sequences of the mature proteins can be easily determined by using the method for the determination of cleavage site of a signal sequence [JP 8-187100 A]. Furthermore, some membrane proteins undergo the processing on the cell surface to be converted to the secreted forms. Such proteins or peptides in the secreted forms shall also come within the scope of the protein of the present invention. In the case where

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sugar chain-binding sites are present in the amino acid sequences of the proteins, expression of the proteins in appropriate eukaryotic cells affords the proteins to which sugar chains are attached. Accordingly, such proteins or peptides to which sugar chains are attached shall also come within the scope of the protein of the present invention.

The DNAs of the present invention include all the DNAs encoding the above-mentioned proteins. These DNAs can be obtained by using a method for chemical synthesis, a method for cDNA cloning and the like.

The cDNAs of the present invention can be cloned, for example, from cDNA libraries derived from the human cells. The cDNAs are synthesized by using poly(A) RNAs extracted from human cells as templates. The human cells may be cells delivered from the human body, for example, by the operation or may be the cultured cells. The cDNAs can be synthesized by using any method such as the Okayama-Berg method [Okayama, H. and Berg, P., Mol. Cell. Biol. 2: 161-170 (1982)], the Gubler-Hoffman method [Gubler, U. and Hoffman, J., Gene 25: 263-269 (1983)] and the like. However, it is desirable to use the capping method [Kato, S. et al., Gene 150: 243-250 (1994)], as exemplified in Examples, in order to obtain a full-length clone in an effective manner. In addition, commercially available human cDNA libraries can be utilized. The cDNAs of the present invention can be cloned from the cDNA libraries by synthesizing an oligonucleotide on the basis of base sequences of any portion in the cDNA of the present invention and screening the cDNA libraries using this oligonucleotide as a probe for colony or plaque hybridization according to a method known in the art. In addition, the cDNA fragments of the present invention can be prepared from an mRNA isolated from human cells by the RT-

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PCR method in which oligonucleotides which hybridize with both termini of the cDNA fragment of interest are synthesized, which are then used as the primers.

The cDNAs of the present invention are characterized in that they comprise any one of the base sequences represented by SEQ ID NOS: 11 to 20, 41 to 50, 71 to 80, 101 to 110, and 131 to 140 or the base sequences represented by SEQ ID NOS: 21 to 30, 51 to 60, 81 to 90, 111 to 120, and 141 to 150. Table 1 summarizes the clone number (HP number), the cells from which the cDNA clone was obtained, the total base number of the cDNA, and the number of the amino acid residues of the encoded protein, for each of the cDNAs.

Table 1

	<del></del>	<del></del>	<del>,                                      </del>	· · · · · · · · · · · · · · · · · · ·
SEQ ID NO	HP	Cells	Base	Number of amino
SEQ ID NO	number	Cells	number	acid residues
1, 11, 21	HP02539	Saos-2	4485	647
2, 12, 22	HP02770	HT-1080	1509	350
3, 13, 23	HP02869	КВ	3059	206
4, 14, 24	HP02956	КВ	2367	213
5, 15, 25	HP02962	КВ	2355	595
6, 16, 26	HP03014	Liver	1024	264
7, 17, 27	HP10608	Saos-2	1237	343
8, 18, 28	HP10609	КВ	1332	244
9, 19, 29	HP10611	кв	1932	303
10, 20, 30	HP10617	HT-1080	1124	160
31, 41, 51	HP02837	HT-1080	4473	1445
32, 42, 52	HP02991	КВ	2630	582
33, 43, 53	HP03063	HT-1080	1472	410
34, 44, 54	HP03091	Liver	1652	483
35, 45, 55	HP03092	Liver	2112	607
36, 46, 56	HP03116	КВ	1087	314
37, 47, 57	HP10618	HT-1080	1694	94
38, 48, 58	HP10619	HT-1080	1522	218
39, 49, 59	HP10622	Liver	1591	460
40, 50, 60	HP10625	Liver	1249	216
61, 71, 81	HP02883	KB	4027	392
62, 72, 82	HP03140	HT-1080	2495	497
63, 73, 83	HP10628	HT-1080	1617	417
64, 74, 84	HP10629	WERI-RB	3269	649
65, 75, 85	HP10635	WERI-RB	458	93
66, 76, 86	HP10636	HT-1080	1712	425
67, 77, 87	HP10640	WERI-RB	1055	149
68, 78, 88	HP10644	WERI-RB	1616	396
69, 79, 89	HP10656	PMA-U937	1860	350
70, 80, 90	HP10672	Thymus	783	153
91, 101, 111	HP03194	кв	3438	303

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92, 102, 112	HP03219	PMA-U937	1144	283
93, 103, 113	HP03236	HT-1080	2339	488
94, 104, 114	HP03237	HT-1080	1765	182
95, 105, 115	HP03267	Liver	1418	184
96, 106, 116	HP03270	PMA-U937	1211	140
97, 107, 117	HP03298	PMA-U937	1099	153
98, 108, 118	HP10631	WERI-RB	3489	173
99, 109, 119	HP10658	HT-1080	931	75
100, 110, 120	HP10663	PMA-U937	1123	159
121, 131, 141	HP03165	KB	3234	636
122, 132, 142	HP03266	HT-1080	2490	318
123, 133, 143	HP03287	Thymus	1465	82
124, 134, 144	HP10665	HT-1080	917	247
125, 135, 145	HP10669	WERI-RB	1306	206
126, 136, 146	HP10670	WERI-RB	2022	432
127, 137, 147	HP10671	Thymus	1227	306
128, 138, 148	HP10673	Thymus	2210	555
129, 139, 149	HP10675	Thymus	1493	250
130, 140, 150	HP10683	PMA-U937	1264	174

The same clones as the cDNAs of the present invention can be easily obtained by screening the cDNA libraries constructed from the human cell lines or human tissues utilized in the present invention using an oligonucleotide probe synthesized on the basis of the base sequence of the cDNA provided in any one of SEQ ID NOS: 11 to 30, 41 to 60, 71 to 90, 101 to 120, and 131 to 150.

In general, the polymorphism due to the individual differences is frequently observed in human genes. Accordingly, any cDNA in which one or plural nucleotides are added, deleted and/or substituted with other nucleotides in SEQ ID NOS: 11 to 30, 41 to 60, 71 to 90, 101 to 120, and 131 to 150 shall come within the scope of the present

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invention.

Similarly, any protein in which one or plural amino acids are added, deleted and/or substituted with other amino acids resulting from the above-mentioned changes shall come within the scope of the present invention, as long as the protein possesses the activity of the protein having any one of the amino acid sequences represented by SEQ ID NOS: 1 to 10, 31 to 40, 61 to 70, 91 to 100, and 121 to 130.

The cDNAs of the present invention also include cDNA fragments (of 10 bp or more) containing any partial base sequence in the base sequences represented by SEQ ID NOS: 11 to 20, 41 to 50, 71 to 80, 101 to 110, and 131 to 140 or in the base sequences represented by SEQ ID NOS: 21 to 30, 51 to 60, 81 to 90, 111 to 120, and 141 to 150. Also, DNA fragments consisting of a sense strand and an anti-sense strand shall come within this scope. These DNA fragments can be utilized as the probes for the genetic diagnosis.

In addition to the activities and uses described above, the polynucleotides and proteins of the present invention may exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

#### Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use;

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as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) identify chromosomes or to map related gene positions: compare with endogenous DNA sequences in patients identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where polynucleotide encodes a protein which binds potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological

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fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

#### Nutritional Uses

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the

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form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

# <u>Cytokine and Cell Proliferation/Differentiation</u> Activity

A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. 137:3494-3500, 1986; Bertagnolli et al., J. 145:1706-1712, 1990; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Bertagnolli, et al., J. Immunol.

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149:3778-3783, 1992; Bowman et al., J. Immunol. 152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon γ, Schreiber, R.D. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

Assays for proliferation and differentiation lymphopoietic cells include, without hematopoietic and limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205al., Nature 336:690-692, 1991; Moreau et Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human interleukin 6-Nordan, R. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11 -Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, limitation, those described in: Current Protocols Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

#### Immune Stimulating or Suppressing Activity

A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including combined immunodeficiency (SCID)), e.q., regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases causes by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania malaria spp. and various fungal infections such

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candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic rheumatoid arthritis, autoimmune erythematosus, pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis, myasthenia graft-versus-host autoimmune and gravis, disease inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly respiratory problems. other allergic asthma) or suppression is desired which immune conditions. in (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an already in progress or may response immune induction of an immune response. The preventing the T cells may be inhibited functions of activated suppressing T cell responses or by inducing tolerance in T cells, or both. Immunosuppression of T cell generally an active, non-antigen-specific, is process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigenspecific and persists after exposure to the tolerizing agent

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has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), e.g., preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result destruction reduced tissue in tissue transplantation. tissue transplants, Typically, in rejection transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (e.g., B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antiqen-blocking reagents may avoid the necessity repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a

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subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

particular blocking reagents efficacy of organ transplant rejection or GVHD can be preventing assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins in vivo as described in Lenschow et al., Science 257:789-792 (1992) and Turka et al., Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function in vivo on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor: ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. efficacy of blocking reagents in preventing or alleviating

autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/lpr/lpr mice or NZB hybrid mice, murine autoimmune arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating useful responses, may also be therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the in vitro activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the

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transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells in vivo.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor lymphoma, sarcoma, melanoma, (e.g., neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides. For cells obtained from a patient can example, tumor transfected ex vivo with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the surface transfected of the peptides on the Alternatively, gene therapy techniques can be used to target a tumor cell for transfection in vivo.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the provides tumor cell the of the surface costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (e.g., a cytoplasmic-domain truncated portion) of an MHC class I  $\alpha$ chain protein and  $\beta$  2 microglobulin protein or an MHC class

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II  $\alpha$  chain protein and an MHC class II  $\beta$  chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated such as the invariant chain, can also cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte orsplenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowmanet al., J.

Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: In vitro antibody production, Mond, J.J. and Brunswick, M. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Thl and CTL responses) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Associates and Wiley-Strober, Pub. Greene Publishing Vitro assays for Mouse (Chapter 3, In Interscience Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994;

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Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

## Hematopoiesis Regulating Activity

A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to

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stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and **CSF** monocytes/macrophages (i.e., traditional useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting megakaryocytes and proliferation of growth consequently of platelets thereby allowing prevention or platelet disorders as treatment of various thrombocytopenia, and generally for use in place of or complementary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the abovementioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without paroxysmal nocturnal anemia and limitation, aplastic hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either in-vivo or conjunction with bone marrow ex-vivo in (i.e., peripheral with progenitor cell transplantation or (homologous or heterologous)) as transplantation cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and

Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without 5 limitation, described in: Methylcellulose colony forming assays, Freshney, M.G. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 1-21, Wiley-Liss, Inc., New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. Allen, T. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland, H.J. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

#### Tissue Growth Activity

A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which cartilage and/or bone growth in circumstances where bone is

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not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. De novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase etc.) mediated by activity, activity, osteoclast inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and

in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by а composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, differentiation of progenitors of tendonligament-forming cells, or induce growth of tendon/ligament cells or progenitors ex vivo for return in vivo to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, i.e. for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head

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trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. W095/16035 (bone, cartilage, tendon);

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International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

# Activin/Inhibin Activity

A protein of the present invention may also exhibit activinorinhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin  $\alpha$ family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin- $\beta$  group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among

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other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

# Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for including, for example, monocytes, cells, mammalian fibroblasts, neutrophils, T-cells, mast cells, eosinophils, endothelial cells. Chemotactic and/or epithelial chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. lymphocytes, attraction of monocytes For example, neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among

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other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. 1744-1748; Gruber et al. J. of 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

### Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke)).

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include,

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without limitation, those described in: Linet et al., J. 26:131-140, 1986; Burdick et al., Clin. Pharmacol. Thrombosis 45:413-419, 1987; Humphrey et Res. al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

## Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors and cell-cell interactions their i.n (including without limitation, cellular adhesion molecules integrins and their ligands) selectins, receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of limitation, (including, without invention the present fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987;

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Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

### Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cellcell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting orpromoting extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

### Tumor Inhibition Activity

In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly

(such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth.

### Other Activities

A protein of the invention may also exhibit one or more 10 activities effects: additional orfollowing of the inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without 15 limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body for example, (such as, size or shape augmentation or diminution, change in bone form or shape); or caricadic cycles orrhythms; effecting biorhythms 20 fertility of male or female subjects; effecting the effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or component(s); nutritional factors or 25 behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of 30 embryonic stem cells in lineages other than hematopoietic

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lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

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### Examples

The present invention is specifically illustrated in more detail by the following Examples, but Examples are not intended to restrict the present invention. procedures with regard to the recombinant DNA and the enzymatic reactions were carried out according to literature ["Molecular Cloning. A Laboratory Manual", Cold Spring Harbor Laboratory, 1989]. Unless otherwise stated, restriction enzymes and various modifying enzymes to be used were those available from Takara Shuzo. The buffer compositions and the reaction conditions for each of the enzyme reactions were as described in the instructions. The cDNA synthesis was carried out according to the literature [Kato, S. et al., Gene 150: (1994)1.

(1) Selection of cDNAs Encoding Proteins Having Hydrophobic Domains

The cDNA library of fibrosarcoma cell line HT-1080 (WO 98/11217), the cDNA library of osteosarcoma cell line Saos-2 (WO 97/33993), the cDNA library of epidermoid carcinoma cell line KB (WO 98/11217) and the cDNA library of liver tissue delivered by the operation (WO 98/21328) were used as the

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cDNA libraries. Additionally, the cDNA libraries constructed from phorbol ester-stimulated histiocytic lymphoma cell line U937 (ATCC CRL 1593) mRNA, human retinoblastoma cell line WERI-RB (ATCC HTB 169) mRNA and human thymus mRNA (Clontech) were also used. Full-length cDNA clones were selected from the respective libraries and the whole base sequences thereof were determined to construct a homo-protein cDNA bank consisting of the full-length cDNA hydrophobicity/hydrophilicity profiles were determined for by the full-length CDNA the proteins encoded registered in the homo-protein cDNA bank by the Kyte-Doolittle method [Kyte, J. & Doolittle, R. F., J. Mol. Biol. 157: 105-132 (1982)] to examine the presence or absence of a hydrophobic region. A clone that has a hydrophobic region being assumed as a secretory signal or a transmembrane domain in the amino acid sequence of the encoded protein was selected as a clone candidate.

# (2) Protein Synthesis by In Vitro Translation

The plasmid vector bearing the cDNA of the present invention was used for in vitro transcription/translation with a  $T_NT$  rabbit reticulocyte lysate kit (Promega). In this case, [35]methionine was added to label the expression product with a radioisotope. Each of the reactions was carried out according to the protocols attached to the kit. Two micrograms of the plasmid was subjected to the reaction at 30°C for 90 minutes in the reaction solution of a total volume of 25  $\mu$ l containing 12.5  $\mu$ l  $\mu$  of  $T_{N}T$ reticulocyte lysate, 0.5  $\mu$ l of a buffer solution (attached 2  $\mu$ l of an amino acid mixture (without to the kit), methionine), 2  $\mu$ l of [ $^{35}$ S]methionine (Amersham) (0.37 MBq/ $\mu$ l), 0.5  $\mu$ l of T7 RNA polymerase, and 20 U of RNasin. The experiment in the presence of a membrane system was carried

out by adding 2.5  $\mu$ l of a canine pancreas microsome fraction (Promega) to the reaction system. To 3  $\mu$ l of the reaction solution was added 2  $\mu$ l of the SDS sampling buffer (125 mM Tris-hydrochloride buffer, pH 6.8, 120 mM 2-mercaptoethanol, 2% SDS solution, 0.025% bromophenol blue and 20% glycerol) and the resulting mixture was heated at 95°C for 3 minutes and then subjected to SDS-polyacrylamide gel electrophoresis. The molecular weight of the translation product was determined by carrying out the autoradiography.

10 (3) Expression in COS7

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Escherichia coli cells harboring the expression vector for the protein of the present invention were cultured at  $37^{\circ}\text{C}$  for 2 hours in 2 ml of the 2xYT culture medium containing  $100~\mu\text{g/ml}$  of ampicillin, the helper phage M13K07 ( $50~\mu$ l) was added, and the cells were then cultured at  $37^{\circ}\text{C}$  overnight. Single-stranded phage particles were obtained by polyethylene glycol precipitation from a supernatant separated by centrifugation. The particles were suspended in  $100~\mu\text{l}$  of 1 mM Tris-0.1 mM EDTA, pH 8 (TE).

The cultured cells derived from monkey kidney, COS7, were cultured at 37°C in the presence of 5% CO<sub>2</sub> in the Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal calf serum. 1 x 10<sup>5</sup> COS7 cells were inoculated into a 6-well plate (Nunc, well diameter: 3 cm) and cultured at 37°C for 22 hours in the presence of 5% CO<sub>2</sub>. After the medium was removed, the cell surface was washed with a phosphate buffer solution followed by DMEM containing 50 mM Tris-hydrochloride (pH 7.5) (TDMEM). A suspension containing 1  $\mu$ l of the single-stranded phage suspension, 0.6 ml of the DMEM medium and 3  $\mu$ l of TRANSFECTAM<sup>TM</sup> (IBF) was added to the cells and the cells were cultured at 37°C for 3 hours in the presence of 5% CO<sub>2</sub>. After the sample solution was removed,

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the cell surface was washed with TDMEM, 2 ml per well of DMEM containing 10% fetal calf serum was added, and the cells were cultured at 37°C for 2 days in the presence of 5% CO<sub>2</sub>. After the medium was exchanged for a medium containing [35S]cystine or [35S]methionine, the cells were cultured for one hour. After the medium and the cells were separated each other by centrifugation, proteins in the medium fraction and the cell membrane fraction were subjected to SDS-PAGE.

## (4) Clone Examples

## 10 <HP02539> (SEQ ID NOS: 1, 11, and 21)

Determination of the whole base sequence of the cDNA insert of clone HP02539 obtained from cDNA library of human osteosarcoma cell Saos-2 line revealed the consisting of a 188-bp 5'-untranslated region, a 1944-bp ORF, and a 2353-bp 3'-untranslated region. The ORF encodes a protein consisting of 647 amino acid residues and there existed a putative secretory signal at the N-terminus and six putative transmembrane domains at the C-terminus. Figure 1 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the mouse frizzled-1 (GenBank Accession No. AF054623). Table 2 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the mouse frizzled-1 Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 90.4% in the entire

region.

# Table 2

	HP	MAEEEAPKKSRAAGGGASWELCAGALSARLTEEGSGDAGGRRRPPVDPRRLARQLLLLLLW
		****.***** * * ****.** * * .**** ****
5	MM	MAEEAAPSESRAA-GRLSLELCAEALPGRREEVGHEDTASHRRPRADPRRWASGLLLLLW
	HP	LLEAPLILGVRAQAAGQGPGQGPGPGQQPPPPPPQQQQSGQQYNGERGISVPDHGYCQPIS
		*********
	MM	LLEAPLLLGVRAQAAGQVSGPGQQAPPPPQPQQSGQQYNGERGISIPDHGYCQPIS
	HP	IPLCTDIAYNQTIMPNLLGHTNQEDAGLEVHQFYPLVKVQCSAELKFFLCSMYAPVCTVL
10		*****
	MM	IPLCTDMAYNQTIMPNLLGHTNQEDAGLEVHQFYPLVKVQCSAELKFFLCSMYAPVCTVL
	HP	EQALPPCRSLCERARQGCEALMNKFGFQWPDTLKCEKFPVHGAGELCVGQNTSDKGTPTP
		************
	MM	EQALPPCRSLCERARQGCEALMNKFGFQWPDTLKCEKFPVHGAGELCVGQNTSDKGTPTP
15	HP	SLLPEFWTSNPQHGGGGHRGGFPGGAGASERGKFSCPRALKVPSYLNYHFLGEKDCGAPC
		******** ***** ***** ***** *****
	MM	${\tt SLLPEFWTSNGQHGGGGYRGGYPGGAGTVERGKFSCPRALRVPSYLNYHFLGEKDCGAPC}$
	HP	EPTKVYGLMYFGPEELRFSRTWIGIWSVLCCASTLFTVLTYLVDMRRFSYPERPIIFLSG
		**********
20	MM	EPTKVYGLMYFGPEELRFSRTWIGIWSVLCCASTLFTVLTYLVDMPRFSYPERPIISLSG
	HP	CYTAVAVAYIAGFLLEDRVVCNDKFAEDGARTVAQGTKKEGCTILFMMLYFFSMASSIWW
		*****************
	MM	CYTAVAVAYIAGFLLEDRVVCNDKFAEDGARTVAQGTNKEGCTILFMMLYFFSMASSIWW
	HP	VILSLTWFLAAGMKWGHEAIEANSQYFHLAAWAVPAIKTITILALGQVDGDVLSGVCFVG
25		***********
	MM	VILSLTWFLAAGMKWGHEAIEANSQYFHLAAWAVPAIKTITILALGQVDGDVLSGVCFLG
	HP	LNNVDALRGFVLAPLFVYLFIGTSFLLAGFVSLFRIRTIMKHDGTKTEKLEKLMVRIGVF
		***********
	MM	LNNVDALRGFVLAPLFVYLFIGTSFLLAGFVSLFRIRTIMKHDGTKTEKLEKLMVRIGVF
30	HP	SVLYTVPATIVIACYFYEQAFRDQWERSWVAQSCKSYAIPCPHLQAGGGAPPHPPMSPDF
		***********
	MM	SVLYTVPATIVIACYFYEQAFRDQWERSWVAQSCKSYAIPCPHLQGGGGVPPHPPMSPDF
	HP	TVFMIKYLMTLIVGITSGFWIWSGKTLNSWRKFYTRLTNSKQGETTV
		******
35	MM	TVFMIKYLMTLNSWRKFYTRLTNSKQGETTV



Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA010020) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

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### <HP02770> (SEQ ID NOS: 2, 12, and 22)

Determination of the whole base sequence of the cDNA insert of clone HP02770 obtained from cDNA library of human fibrosarcoma cell line HT-1080 revealed the structure consisting of a 252-bp 5'-untranslated region, a 1053-bp ORF, and a 204-bp 3'-untranslated region. The ORF encodes a protein consisting of 350 amino acid residues and there existed two putative transmembrane domains. Figure 2 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 42 kDa that was somewhat larger than the molecular weight of 38,274 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human RING zinc finger protein (GenBank Accession No. AF037204). Table 3 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the human RING zinc finger protein (ZN). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue

similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 56.0% in the entire region.

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Table 3

MHPAAFPLPVVVAAVLWGAAPTRGLIRATSDHNASMDFADLPALFGATLS HP ZN MLLSIGMLMLSATQVYTILTVQLFAFLNLLPVEADILAYNFENASQTFDDLPARFGYRLP HP QEGLQGFLVEAHPDNACSPIAPPPPAPVNGSVFIALLRRFDCNFDLKVLNAQKAGYGAAV 10 ....\*\*.\*.\*\*\*\*\* \*\*\* \*\*\* \*\*\* \*\*\* \*\* ZN AEGLKGFLINSKPENACEPIVPPPVKDNSSGTFIVLIRRLDCNFDIKVLNAQRAGYKAAI HP VHNVNSNELLNMVWNSEEIQQQIWIPSVFIGERSSEYLRALFVYEKGARVLLVPDNTFPL ZN VHNVDSDDLISMGSNDIEVLKKIDIPSVFIGESSANSLKDEFTYEKGGHLILVPEFSLPL 15 HP GYYLIPFTGIVGLLVLAMGAVMIARCIQHRKRLQRNRLTKEQLKQIPTHDYQKGDQYDVC \*\*\*\*\*\* \*\*\* \*\*\* ZN EYYLIPFLIIVGICLILIVIFMITKFVQDRHRARRNRLRKDQLKKLPVHKFKKGDEYDVC HP AICLDEYEDGDKLRVLPCAHAYHSRCVDPWLTQTRKTCPICKQPVHRGPGDED-QEEETQ \*\*\*\*\*\*\*\*\*\* 20 ZN AICLDEYEDGDKLRILPCSHAYHCKCVDPWLTKTKKTCPVCKQKVVPSQGDSDSDTDSSQ HP GQEEGDEGEPRDHPASERTPLLGSSPTLPTSFGSLAPAPLVFPGPSTDPPLSPPSSPVIL ...\* .\* .\* .\* ZN EENEVTEHTPLLRPLASVSAQSFGALSESRSHQNMTESSDYEEDDNEDTDSSDAENEINE 25 HP V ZN HDVVVQLQPNGERDYNIANTV

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA434312) among ESTs. However, since they are partial sequences, it can not be judged whether or

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not they encode the same protein as the protein of the present invention.

<HP02869> (SEQ ID NOS: 3, 13, and 23)

Determination of the whole base sequence of the cDNA insert of clone HP02869 obtained from cDNA library of human epidermoid carcinoma cell line KB revealed the structure consisting of a 229-bp 5'-untranslated region, a 621-bp ORF, and a 2209-bp 3'-untranslated region. The ORF encodes a protein consisting of 206 amino acid residues and there existed two putative transmembrane domains. Figure 3 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 22 kDa that was almost identical with the molecular weight of 22,367 predicted from the ORF.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA278247) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

### 25 <HP02956> (SEQ ID NOS: 4, 14, and 24)

Determination of the whole base sequence of the cDNA insert of clone HP02956 obtained from cDNA library of human epidermoid carcinoma cell line KB revealed the structure consisting of a 68-bp 5'-untranslated region, a 642-bp ORF, and a 1657-bp 3'-untranslated region. The ORF encodes a protein consisting of 213 amino acid residues and there existed three putative transmembrane domains. Figure 4

depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 22 kDa that was almost identical with the molecular weight of 23,902 predicted from the ORF. When expressed in COS7 cells, an expression product of about 20 kDa was observed in the membrane fraction.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human tetraspan NET-4 (GenBank Accession No. AF065389). Table 4 shows the comparison, between amino acid sequences of the human protein of the present invention (HP) and the human tetraspan NET-4 (TS). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 58.8% in the C-terminal region of 119 amino acid residues.

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#### Table 4

HP MHY TS MSGKHYKGPEVSCCIKYFIFGFNVIFWFLGITFLGIGLWAWNEKGVLSNISSITDLGGFD 5 HP YRYSNAKVSCWYKYLLFSYNIIFWLAGVVFLGVGLWAWSEKGVLSDLTKVTRMHGIDPVV TS PVWLFLVVGGVMFILGFAGCIGALRENTFLLKFFSVFLGIIFFLELTAGVLAFVFKDWIK HP LVLMVGVVMFTLGFAGCVGALRENICLLNFNQCCGAYGPEDWDLNVYFNCSGASYSREKC 10 .. \*\*\*\*.\*..\*.\*\*.\*\* TS DQLYFFINNNIRAYRDDIDLQNLIDFTQEYWQCCGAFGADDWNLNIYFNCTDSNASRERC HP GVPFSCCVPDPAQKVVNTQCGYDVRIQLKSKWDESIFTKGCIQALESWLPRNIYIVAGVF TS GVPFSCCTKDPAEDVINTQCGYDARQKPEVDQQIVIYTKGCVPQFEKWLQDNLTIVAGIF 15 HP IAISLLQIFGIFLARTLISDIEAVKAGHHF \*.\*.\*\*\*\*\*\* \*\*..\*.\*\*\*\*\* TS IGIALLQIFGICLAQNLVSDIEAVRASW

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. T05279) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP02962> (SEQ ID NOS: 5, 15, and 25)

Determination of the whole base sequence of the cDNA insert of clone HP02962 obtained from cDNA library of human epidermoid carcinoma cell line KB revealed the structure consisting of a 19-bp 5'-untranslated region, a 1788-bp ORF, and a 548-bp 3'-untranslated region. The ORF encodes a

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protein consisting of 595 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 5 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the protein. In vitro translation resulted in formation of a translation product of 70 kDa that was somewhat larger than the molecular weight of 67,549 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 85 kDa to which sugar chains are presumably attached. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from alanine at position 23. In addition, there exist in the amino acid sequence of this protein four sites at which Nglycosylation may occur (Asn-Thr-Thr at position 75, Asn-Gln-Thr at position 153, Asn-Tyr-Thr at position 237 and Asn-Ser-Ser at position 360).

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human hypothetical protein KIAA0584 (GenBank Accession No. AB011156). Table 5 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the human hypothetical protein KIAA0584 (KI). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 52.9% in the entire region.

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# Table 5

	HP	MRAARAAPLLQLLLLLGPWLEAAGVAESPLPAVVLAILARNAEHSL
		* **** * .* . * .* .* .* .* .* .*
5	KI	LAWSLLLLSSALLREGCRARFVAERDSEDDGEEPVVFPESPLQSPTVLVAVLARNAAHTL
	HP	PHYLGALERLDYPRARMALWCATDHNVDNTTEMLQEWLAAVGDDYAAVVWRPEGEPRFYP
		**.** ******** * ******* * * * *
	KI	PHFLGCLERLDYPKSRMAIWAATDHNVDNTTEIFREWLKNVQRLYHYVEWRPMDEPESYP
	HP	DEEGPKHWTKERHQFLMELKQEALTFAR-NWGADYILFADTDNILTNNQTLRLLMGQGLP
10		** **** * . * . * . * . * . * . *
	KI	DEIGPKHWPTSRFAHVMKLRQAALRTAREKW-SDYILFIDVDNFLTNPQTLNLLIAENKT
	HP	VVAPMLDSQTYYSNFWCGITPQGYYRRTAEYFPTKNRQRRGCFRVPMVHSTFLASLRAEG
		******.*. ********* *** *** *** *** ***
	KI	IVAPMLESRGLYSNFWCGITPKGFYKRTPDYVQIREWKRTGCFPVPMVHSTFLIDLRKEA
15	HP	ADQLAFYPPHPNYTWPFDDIIVFAYACQAAGVSVHVCNEHRYGYMNVPVKSHQGLEDERV
		***************************************
	KI	SDKLTFYPPHQDYTWTFDDIIVFAFSSRQAGIQMYLCNREHYGYLPIPLKPHQTLQEDIE
	HP	NFIHLILEALVDGPRMQASAHVTRPSKRPSKIGFDEVFVISLARRPDRRERMLASLWEME
		*.***** *.*** *.*.*.*.*.*.* .*
20	KI	NLIHVQIEAMIDRPPMEPSQYVSVVPKYPDKMGFDEIFMINLKRRKDRRDRMLRTLYEQE
	HP	ISGRVVDAVDGWMLNSSAIRNLGVDLLPGYQDPYSGRTLTKGEVGCFLSHYSIWEEVVAR
		**.*** **.******.*.*.*.*.*.*.
	KI	IEVKIVEAVDGKALNTSQLKALNIEMLPGYRDPYSSRPLTRGEIGCFLSHYSVWKEVIDR
	HP	GLARVLVFEDDVRFESNFRGRLERLMEDVEAEKLSWDLIYLGRKQVN-PEKETAVEGLPG
25		****.****** .** .** * **** * *.**
	KI	ELEKTLVIEDDVRFEHQFKKKLMKLMDNIDQAQLDWELIYIGRKRMQVKEPEKAVPNVAN
	HP	LVVAGYSYWTLAYALRLAGARKILASQPLRRMLPVDEFLPIMFDQHPNEQYKAHFWPRDL
		** *.*****.**.**
		LVEADYSYWTLGYVISLEGAQKLVGANPFGKMLPVDEFLPVMYNKHPVAEYKEYYESRDL
30	HP	VAFSAQPLLAAPTHYAGDAEWLSDTETSSPWDDDSGRLISWSGSQKTLRSPRLDLTGS
		****.** ****.******** **
		KAFSAEPLLIYPTHYTGQPGYLSDTETSTIWDNETV-ATDWDRTHAWKSRKQSRIYSNAK
	HP	SGHSLQPQPRDEL
		••••
35	KI	NTEALPPPTSLDTVPSRDEL

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA358896) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

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## <HP03014> (SEQ ID NOS: 6, 16, and 26)

Determination of the whole base sequence of the cDNA insert of clone HP03014 obtained from cDNA library of human liver revealed the structure consisting of a 26-bp 5'and a 203-bp untranslated region, a 795-bp ORF, untranslated region. The ORF encodes a protein consisting of 264 amino acid residues and there existed one putative depicts Figure 6 domain. transmembrane hydrophobicity/hydrophilicity profile, obtained by the Kytethe present protein. Doolittle method, of translation resulted in formation of a translation product of 31 kDa that was somewhat larger than the molecular weight of 28,471 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the mouse WW domain-binding protein 1 (GenBank Accession No. U40825). Table 6 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the mouse WW domain-binding protein 1 (MM). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue

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similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 85.1% in the entire region.

5 Table 6

ΗP MVASAKMGRAGTMAVAAELR MM MARASSRNSSEEAWGSLQAPQQQQSPAASSLEGAIWRRAGTQTRALDTILYHPQQSHLLR 10 HP ELCPGVNNQPYLCESGHCCGETGCCTYYYELWWFWLLWTVLILFSCCCAFRHRRAKLRLQ \*\*\*\*\*\*\*\*\*\*\*\*\*\* MM ELCPGVNTQPYLCETGHCCGETGCCTYYYELWWFWLLWTVLILFSCCCAFRHRRAKLRLQ HP OOOROREINLLAYHGACHGAGPFPTGSLLDLRFLSTFKPPAYEDVVHRPGTPPPPYTVAP \*\*\*\*\*\*\*\*\*\* 15 MM QOQROREINLLAYHGACHGAGPVPTGSLLDLRLLSAFKPPAYEDVVHHPGTPPPPYTVGP HP GRPLTASSEQTCCSSSSSCPAHFEGTNVEGVSSHQSAPPHQEGEPGAGVTPASTPPSCRY \* \* \*,\*\*\* \* \*\*\*,\*\*\*,\*\*,\*\*,\*\*\*\*\*\*,\*\*\* \*\*\*\*\* \*\*,..., .\*\* MM GYPWTTSSECTRCSSESSCSAHLEGTNVEGVSSQOSALPHQEGEPRAGLSPVHIPPSCRY HP RRLTGDSGIELCPCPASGEGEPVKEVRVSATLPDLEDYSPCALPPESVPQIFPMGLSSSE 20 \*\*\*\*\*\*\*\*\*\*\*\*\* MM RRLTGDSGIELCPCPDSSEGEPLKEARASASQPDLEDHSPCALPPDSVSQVPPMGLASSC HP GDIP MM GTSHK

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. W24575) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

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<HP10608> (SEQ ID NOS: 7, 17, and 27)

Determination of the whole base sequence of the cDNA insert of clone HP10608 obtained from cDNA library of human the line Saos-2 revealed osteosarcoma cell consisting of a 23-bp 5'-untranslated region, a 1032-bp ORF, and a 182-bp 3'-untranslated region. The ORF encodes a protein consisting of 343 amino acid residues and there existed five putative transmembrane domains. Figure depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 37 kDa that was somewhat smaller than the molecular weight of 40,584 predicted from the ORF. When expressed in COS7 cells, an expression product of about 36 kDa was observed in the membrane fraction.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. T35406) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10609> (SEQ ID NOS: 8, 18, and 28)

Determination of the whole base sequence of the cDNA insert of clone HP10609 obtained from cDNA library of the human epidermoid carcinoma cell line KB revealed the structure consisting of a 38-bp 5'-untranslated region, a 735-bp ORF, and a 559-bp 3'-untranslated region. The ORF encodes a protein consisting of 244 amino acid residues and there existed one putative transmembrane domain at the N-terminus. Figure 8 depicts the hydrophobicity/hydrophilicity

profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 27 kDa that was almost identical with the molecular weight of 27,756 predicted from the ORF. When expressed in COS7 cells, an expression product of about 26 kDa was observed in the membrane fraction.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the Mycobacterium tuberculosis hypothetical protein Rv1147 (GenBank Accession No. Z95584). Table 7 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the Mycobacterium tuberculosis hypothetical protein Rv1147 (MT). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 31.7% in the entire region.

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#### Table 7

HP	MDILVPLLQLLVLLLTLPLHLMALLGCWQPLCKSYFPYLMAVLTPKSNRKMESKKRELFS
MT	MTSGAAASASRVDHPLFARIWPVVAAHEAEAIRAL
HP	QIKGLTGASGKVALLELGCGTGANFQFYPPGC-RVTCLDPNPHFEKFLTKSMAENRHLQY
	*.* **.* **.* *.*.**** * *
MT	RRENLAGLSGRVLEVGAGVGTNFAYYPVAVEQVIAMEPEPRLAA-KARIAAADAPVPI
HP	ERFVVAPGEDMRQLADGSMDVVVCTLVLCSVQSPRKVLQEVRRVLRPGGVLFFWEHVAEP
	* . *
TM	-VVTDKTVEEFRDTETFDAVVCSLVLCSVSDPGAVLAHLRSLLRRGGELRYLEHVASA
HP	YGSWAFMWQQVFEPTWKHIGDGCCLTRETWKDLENAQFSEIQMERQPPPLKWLPVGPH
	* * * * *.** * * * ***.
MT	-GARGRVQRFVDATFWPRLAGNCHTHRHTERAILDAGFVVDSSRREWAFPAWVPLPVSEL
HP	IMGKAVK
	***
MT	ALGRAHRT

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. T60981) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10611> (SEQ ID NOS: 9, 19, and 29)

Determination of the whole base sequence of the cDNA insert of clone HP10611 obtained from cDNA library of the human epidermoid carcinoma cell line KB revealed the structure consisting of a 37-bp 5'-untranslated region, a 912-bp ORF, and a 983-bp 3'-untranslated region. The ORF

encodes a protein consisting of 303 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 9 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 31 kDa that was somewhat smaller than the molecular weight of 33,856 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 36 kDa. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from leucine at position 34. When expressed in COS7 cells, an expression product of about 35 kDa was observed in the membrane fraction.

The search of the protein data base using the amino acid sequence of the present protein revealed that the 218 amino acid residues at the C-terminus of the protein matched with the amino acid sequence of human glucosidase II (SWISS-PROT Accession No. Q06003). However, no similarity was observed at the N-terminal portion.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. H14054) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

# <HP10617> (SEQ ID NOS: 10, 20, and 30)

Determination of the whole base sequence of the cDNA insert of clone HP10617 obtained from cDNA library of the human fibrosarcoma cell line HT-1080 revealed the structure

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consisting of a 72-bp 5'-untranslated region, a 483-bp ORF, and a 569-bp 3'-untranslated region. The ORF encodes a protein consisting of 160 amino acid residues and there existed four putative transmembrane domains. Figure 10 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight. When expressed in COS7 cells, an expression product of about 17 kDa was observed in the membrane fraction.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. H67672) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP02837> (SEQ ID NOS: 31, 41, and 51)

Determination of the whole base sequence of the cDNA insert of clone HP02837 obtained from cDNA library of human fibrosarcoma cell line HT-1080 revealed the structure consisting of a 44-bp 5'-untranslated region, a 4338-bp ORF, and a 91-bp 3'-untranslated region. The ORF encodes a protein consisting of 1445 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 11 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 150 kDa that was almost identical with the molecular weight of 161,657 predicted from the ORF. Application of the (-3,-1) rule, a method for predicting the

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cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from valine at position 22. In addition, there exist in the amino acid sequence of this protein 18 sites at which N-glycosylation may occur.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human  $\alpha$ -2 macroglobulin (SWISS-PROT Accession No. P01023). Table 8 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the human  $\alpha$ -2 macroglobulin (MG). Therein, the marks of - and \* represent a gap and an amino acid residue identical with that of the protein of the present invention, respectively. The both proteins shared a homology of 29.5% in the entire region.

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# Table 8

	HP	MQGPPLLTAAHLLCVCTAALA-VAPGPRFLVTAPGIIRPGGNVTIGVELLEHCPSQVT
		* ** ** * * * * * * * *
5	MG	MGKNKLLHPSLVLLLLVLLPTDASVSGKPQYMVLVP-SLLHTETTEKGCVLLSYLNETVT
	HP	VKAELLKTASN-LTVSVLEAE-GVFEKGSFKTLTLPSLPLNSADEIYELRVTGRTQDEIL
		* * * * * * * * * * * * * * * * * * * *
	MG	VSASLESVRGNRSLFTDLEAENDVLHCVAFAVPKSSSNEEVMFLTVQVKGPTQE
	HP	FSNSTRLSFETKRISVFIQTDKALYKPKQEVKFRIVTLFSDFKPYKTSLNILIKDPKS
10		* * **** *** * * * * * * * * * *
	MG	FKKRTTVMVKNEDSLVFVQTDKSIYKPGQTVKFRVVSMDENFHP-LNELIPLVYIQDPKG
	HP	NLIQQWLSQQSDLGVISKTFQLSSHPILGDWSIQVQ-VNDQTYYQSFQVSEYVLPKFEVT
		* * * * * * * * * * * * * * * * * * * *
	MG	NRIAQWQSFQLEGGLKQFSFPLSSEPFQGSYKVVVQKKSGGRTEHPFTVEEFVLPKFEVQ
15		LQTPLYCSMNSKHLNGTITAKYTYGKPVKGDVTLTFLPLSFWGKKKNITKTFKING
10		* * ****** * **
	MG	VTVPKIITILEEEMNVSVCGLYTYGKPVPGHVTVSICRKYSDASDCHGEDSQAFCEKFSG
		SANFSFNDEEMKNVMDSSNGLSEY-LDLSFPGPVEILTTVTESVTGISRNVSTNVF
		* ** * ** * * *
20	MG	QLNSHGCFYQQVKTKVFQLKRKEYEMKLHTEAQIQEEGTVVELTGRQSSEITRTITKLSF
20		FKQHDYIIEFFDYTTVLKPSLNFTATVKVTRADGNQLTLEERRNNVVITVTQRNYTEY
		* * * * * * * *
	MG	VKVDSHFRQGIPFFGQVRLVDGKGVPIPNKVIFIRGNEANYYSNATTDEHGLV
		WSGSNSGNQKMEAVQKINYTVPQSGTFKIEFPILEDSSELQLKAYFLGSKSSMAVHSLFK
25	111	* * * * * * * * * * * * * *
20	MG	QFSINTTN-VMGTSLTVRVNYKDRSPCYGYQWVSEEHEEAHHTAYLVFSPSKSFVHLEPM
		SPSKTYIQLKTRDENIKVGSPFELVVSGNKRLKELSYMVVSRGQLVAVGKQNSTMF
	nr	* * * * * * * * * * *
	MC	SHELPCGHTQTVQAHYILNGGTLLGLKKLSFYYLIMAKGGIVRTGTHGLLVKQEDMKGHF
00		S-LTPENS-WTPKACVIVYYIEDDGEIISDVLKIPVQLVFKNKIKLYWSKVKAEPSEKVS
30	пP	* * * * * * * * * * * * * * * * * * *
		SISIPVKSDIAPVARLLIYAVLPTGDVIGDSAKYDVENCLANKVDLSFSPSQSLPASHAH
	HP	LRISVT-QPDSIVGIVAVDKSVNLMNASNDITMENVVHEL-ELYNTG
		** ** * * ** ** * * * * * * *
25	MG	I.R VTAA POSVCALRAVDOSVLIMKPDAELSASSVYNLLPEKDLTGFPGPLNDQDDEDC

	HI	P -			YY.	LGM	ŒMI	NSF	'AVF	QE	-C	GLI	WVI	TD	AN.	L	-TI	(DY	IDG	VY.	DN	AEY	AEF	LFME	ENE
					*	*				*			*	*	,	*	*		*					*	* *
	MC	3 I	NRF	INV	YI	NGI	TY:	rpv	SSI	NE	KD	MY	SFI	EDI	MG)	LKA	FTI	ISK	IRK	PK	MCI	PQL	QQY	EMH	GPE
	HI	? н	IV-				I	DIH	DFS	LG	SS	PH-		VRI	KHI	FPE	TWI	WL.	DTN	MG	SRI	QYI	EFE	VTV.	PDSI
5			*									**		**:	<b>*</b> :	***	***	*		,	*		*	***	** *
	MO	3 Li	RVG	FY.	ESI	DVM	GRO	3HA	RLV	HV	EE:	PHI	CET	VRI	(YI	PE	TWI	WD:	LVV	VNS	SAG	VA	EVG	VTV	PDTI
	HE	? <b>T</b> :	SWV	AT	GF1	VIS	EDI	GL	GLT	TT:	PV	ELζ	QAF	QPI	F	FL	NLP	YS	VIR	GEI	EFA	LE:	ITI	FNY	LKDA
		*	*	*	*	*	**	**	*	*		*	**	***	r <b>*</b>	*	*	**	***	**	*	*	*	**	*
	MG	T	EWK	AG	AFC	CLS	EDA	\GL	GIS	ST-	-A:	SLF	LAF	QPF	ΈV	EL:	<b>IMP</b>	YS	JIR	GE <i>I</i>	¥Τ	LK	ATV.	LNY.	LPKC
10	HP	<b>T</b> 1	EVK	VI:	IEF	KSD	KFI	IL	MTS	SE-			-IN	ATG	HÇ	2-Q'	rl.L	VP:	SED	GAJ	ľVI	FP:	IRP	THL.	GE
			*	*	*	*	*			*			*	* *		•		*			*	*		*	*
	MG	; II	RVS	VQI	LEA	ASP.	AFI	.AV	PVE	ΚEÇ	QA J	PHC	:IC	ANG	RÇ	YTV:	SWA	VTI	PKS	LGN	IVN	FTV	/SAI	EAL	ESQE
	HP	· II	PIT	VT	ALS	SP-	-TA	SD	AIT	QM]	[L]	ЛKA	EG:	IEK	SY	SQS	SIL	LDI	TDI	VRI	.QS	TLE	CTL:	SFS1	PPN
			*			*		*			**	k	**	**	•		*	*					*:	k	***
15	MG	LC	CGT	EVI	?sv	PE	HGR	KD'	rvi	KPI	LV	ÆΡ	EG)	LEK	ΕT	TFI	1SL	L	-CI	?SG	GE	VSE	EELS	SLKI	PPN
	HP	TV	/TG	SEF	QV9	)IT	AIG	DVI	LGPS	SIN	IGI	AS	LII	RMP	YG	CGE	EQNI	MIN	FAI	PNI	YI	LDY	LTI	ΚΚΚÇ	OLTO
		*	r :	* *	•		*	* 1	* *				*	**	**	***	**	*	***	**	*	* * *	*	4	**
	MG	V	ÆE:	SAF	<b>LAS</b>	VSV	/LG	DII	LGS2	AMÇ	IN(	'QN	LL	2MP	YG	CGE	QNI	MVI	FAI	NI	YV.	LDY	LNE	ETQÇ	LTP
	HP	NI	KE	KAI	SF	MRζ	QGY	QRE	ELLY	/QR	ED	GS	FS!	<b>\F</b> G		NYL	PS	3SI	WLS	AF	VL	RCF	LEA	<b>IDP</b> Y	IDI
20			* :	* *			**	**	* *	t	*	**	*	**			1	k *	**	**	**	*	. ,	. *	* *
	MG	EV	'KSI	KAI	GY	LNI	rgy (	QRÇ	ZLNY	KH	YD	GS	YSI	rfG	ER	YGR	NQC	GNT	WLI	'AF	VL	KTF	AQA	RAY	IFI
	HP	DQ	NVI	LHR	TY	TWI	LKG	HQK	SNO	EF	WD	PG	RVI	HS	EL	QGG	NKS	SPV	TLT	'AY	IV:	rsl	LGY	RKY	QPN
		*				**	t	**	**	*		*				**	_	*	**	**	*	*	*		
	MG	DE	AH]	QT	AL:	IWI	SQI	RQK	DNG	CF	RS	SG	SLI	NN	AII	KGG	VEI	EV	TLS	AY:	IT]	[AL	LEI	PLT	VTH
25	HP	ID	VQE	ESI	HF:	LES			-EF	'SR	GI	SDI	IYV.	LA	CI:	ΓΥA	LSS	VG	-SP	KA	KE.	LN	MLT	WRA	EQE
			*		,	***	,		*		*	*	**	* *	k	**		*		* :	**	*	*	*	
	MG	PV	VRN	IAL.	FC	LES	AWI	KTA	QEG	DH	G-	SH	ΛΥΊ	KAI	LL	AYA	FAI	AG	NQD	KRI	KEV	/LK	SLN	EEA	VKK
	HP	GG	MQF	W-		V	SSI	ESK	LSD	SW	QP:	RSI	DΙ	EV	\A)	ZAL	LSH	FL	QFQ	9	rse	:	G	IPI	MRW
				*						,	*	*		*	4	* *	*			1	***	•		*	*
30	MG	DN	SVH	WE	RΡÇ	QKΡ	KAI	PVG	HFY	EP(	QAI	PS <i>I</i>	ŒV	EM]	rsi	(VL	LAY	LT	AQP	AP'I	rse	DL:	rsa'	TNI	VKW
	HP	LS	RQR	NS]	LGC	<b>FA</b>	STÇ	DT'	TVA	LK	AL:	SEF	'AA	LM	1TE	ERTI	QIØ	VIV	/TG	PSS	5-P	SP	ЖF.	LID:	THN
			*	*	* *	t #	***	**	**	* :	**:	*	*		*	**		1	*	* *	t		**	*	*
	MG	ITI	KQQ	NA(	QGG	FS	STÇ	DT	VVA	LHA	ALS	SKY	GA	ATF	'T-	RT(	3KA	7QA	TI	QSS	GT	FSS	SKF	QVDI	NNN
	HP	RLI	LLQ	TAI	ELA	VV	QPI	'AV	NIS.	ANC	3F(	GF <i>A</i>	IC	QLN	IVV	YNY	/ΚΑ	SGS	SRI	RRR	RSI	QNÇ	QEA!	FDLI	OVA
35		**1	***		*		*			4		k		*		**								*	

	MG	RLLL	.QQVS	L-PI	ELP(	EYS	MKVT	GEGC	YYLQ	TSLKY	N	- 11121	EKEEFF	'L'ATIGA	ĞLUPĞL
	HP	VKEN	K-DD	LNH	NDLI	WCI	SFSGI	PGRS	LAME	MEVNI	LSGF	<b>IVPS</b> I	EAISLS	ETVKK	VEYDHG
		*	*		*	*	*	*	**	*	***		* *	***	*
	MG	CDEP	KAHI	SFQ	SLS	vsy	TGS-I	RSASI	MAI'	VDVKM	IVSGF		IPLK	(PTVKM	LE
5	HP	KLNL	YLDS	VNE	rqf	ZVNI	PAVRI	NFKV:	QTM3	DASVS	YOU	YEPRI	RQAVRS	YNSEV	KLSSCD
				* *	k	*		**1	* *		*	*	**		*
	MG		RSNH	VSR1	revs	SNH	VLIYI	LDKV	SNQT:	LSLFF	'TVLQI	OVP	VR-	,	D
	HP	LCSD	VQGC	RPCE	EDGI	SGS	HHHSS	SVIF	FCF:	KLLYF	'MELWI	_			
		*			*				*	* *					
10	MG	L	KPAI	VKV	YDY	ETD	EFAI <i>l</i>	AEYN!	APCS:	KDL	GN	A			

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. W33075) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

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# <HP02991> (SEQ ID NOS: 32, 42, and 52)

Determination of the whole base sequence of the cDNA insert of clone HP02991 obtained from cDNA library of human epidermoid carcinoma cell line KB revealed the structure consisting of a 81-bp 5'-untranslated region, a 1749-bp ORF, and a 800-bp 3'-untranslated region. The ORF encodes a protein consisting of 582 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 12 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 66 kDa that was somewhat larger than the molecular weight of 64,244 predicted from the ORF. In

this case, the addition of a microsome led to the formation of a product of 78 kDa to which sugar chains are presumably attached. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from valine at position 27. In addition, there exist in the amino acid sequence of this protein seven sites at which N-glycosylation may occur (Asn-Gly-Thr at position 70, Asn-Gly-Thr at position 182, Asn-Gly-Ser at position 294, Asn-His-Thr at position 310, Asn-Gly-Thr at position 352, Asn-Glu-Thr at position 393 and Asn-Cys-Ser at position 407).

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the mouse FKBP65-binding protein (GenBank Accession No. L07063). Table 9 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the mouse FKBP65-binding protein (MM). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 88.8% in the entire region.

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# Table 9

	HP	${\tt MFPAGPPSHSLLRLPLLQLLLLVVQAVGRGLGRASPAGGPLEDVVIERYHIPRACPREVQ}$
		** .** ** * *
5	MM	${\tt MFLVGSSSHTLHRVRILPLLLL-LQTLERGLGRASPAGAPLEDVVIERYHIPRACPREVQ}$
	HP	${\tt MGDFVRYHYNGTFEDGKKFDSSYDRNTLVAIVVGVGRLITGMDRGLMGMCVNERRRLIVP}$
		***********
	MM	${\tt MGDFVRYHYNGTFEDGKKFDSSYDRSTLVAIVVGVGRLITGMDRGLMGMCVNERRRLIVP}$
	HP	PHLGYGSIGLAGLIPPDATLYFDVVLLDVWNKEDTVQVSTLLRPPHCPRMVQDGDFVRYH
10		***********************
	MM	PHLGYGSIGVAGLIPPDATLYFDVVLLDVWNKADTVQSTILLRPPYCPRMVQNSDFVRYH
	HP	YNGTLLDGTSFDTSYSKGGTYDTYVGSGWLIKGMDQGLLGMCPGERRKIIIPPFLAYGEK
		*************
	MM	YNGTLLDGTGFDNSYSRGGTYDTYIGSGWLIKGMDQGLLGMCPGEKRKIIIPPFLAYGEK
15	HP	GYGTVIPPQASLVFHVLLIDVHNPKDAVQLETLELPPGCVRRAGAGDFMRYHYNGSLMDG
		************
	MM	${\tt GYGTVIPPQASLVFYVLLLDVHNPKDTVQLETLELPQGCVRRAVAGDFMRYHYNGSLMDG}$
	HP	TLFDSSYSRNHTYNTYIGQGYIIPGMDQGLQGACMGERRRITIPPHLAYGENGTGDKIPG
		************
20	MM	TLFDSSYSRNHTYNTYVGQGYIIPGMDQGLQGACIGERRRITVPPHLAYGENGTGDKIPG
	HP	SAVLIFNVHVIDFHNPADVVEIRTLSRPSETCNETTKLGDFVRYHYNCSLLDGTQLFTSH
		************
	MM	SAVLIFDVHVIDFHNPSDPVEIKTLSRPPENCNETSKIGDFIRYHYNCSLLDGTRLFSSH
	HP	DYGAPQEATLGANKVIEGLDTGLQGMCVGERRQLIVPPHLAHGESGARGVPGSAVLLFEV
25		****** ********** ******
	MM	DYEAPQEITLGANKVIEGLDRGLQGMCVGERRQLIVPPHLAHGENGARGVPGSAVLLFEV
	HP	ELVSREDGLPTGYLFVWHKDPPANLFEDMDLNKDGEVPPEEFSTFIKAQVSEGKGRLMPG
		***********
	MM	ELVSREDGLPTGYLFVWYQDPSTSLFEDMDLNKDGEVPPEEFSSFIKAQVNEGKGRLMPG
30	HP	QDPEKTIGDMFQNQDRNQDGKITVDELKLKSDEDEERVHEEL
		************
	MM	ODPDKTISDMFONODRNODGKITAEELKLKSDEDQERVHEEL

Furthermore, the search of the GenBank using the base

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sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA308536) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

# <HP03063> (SEQ ID NOS: 33, 43, and 53)

Determination of the whole base sequence of the cDNA insert of clone HP03063 obtained from cDNA library of human line HT-1080 fibrosarcoma cell revealed the structure consisting of a 88-bp 5'-untranslated region, a 1233-bp ORF, and a 151-bp 3'-untranslated region. The ORF encodes a protein consisting of 410 amino acid residues and there existed a putative transmembrane domain at the N-terminus. Figure 13 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 46 kDa that was almost identical with the molecular weight of 45,786 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the mouse AUP1 (GenBank Accession No. U41736). Table 10 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the mouse AUP1 (MM). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 90.2% in the entire region.

## Table 10

	HP	MELPSGPGPERLFDSHRLPGDCFLLLVLLLYAPVGFCLLVLRLFLGIHVFLVSCALPDSV
		** * ********* . * **** . * **** . * ***** . *
5	MM	MEPPPAPGPERLFDSHRLPSDGFLLLALLLYAPVGLCLLVLRLFLGLHVFLVSCALPDSV
	HP	LRRFVVRTMCAVLGLVARQEDSGLRDHSVRVLISNHVTPFDHNIVNLLTTCSTPLLNSPP
		*************
	MM	LRRFVVRTMCAVLGLVARQEDSGLRDHRVRVLISNHVTPFDHNIVNLLTTCSTPLLNSPP
	HP	SFVCWSRGFMEMNGRGELVESLKRFCASTRLPPTPLLLFPEEEATNGREGLLRFSSWPFS
10		********
	MM	SFVCWSRGFMEMDRRVELVESLKKFCASTRLPPTPLLLFPEEEATNGREGLLRFSSWPFS
	HP	IQDVVQPLTLQVQRPLVSVTVSDASWVSELLWSLFVPFTVYQVRWLRPVHRQLGEANEEF
		***********
	MM	IQDVVQPLTLQVQRPLVSVTVSDASWVSELLWSLFVPFTVYQVRWLHPIRRQLGEESEEF
15	HP	ALRVQQLVAKELGQTGTRLTPADKAEHMKRQRHPRLRPQSAQSSFPPSPGPSPDVQLATL
		****************
	MM	ALRVQQLVAKELGQIGTRLTPADKAEHMKRQRHPRLRPQSVQSSFPSPPSPSSDVQLTTL
	HP	AQRVKEVLPHVPLGVIQRDLAKTGCVDLTITNLLEGAVAFMPEDITKGTQSLPTASASKF
		**************
20	MM	AHRVKEVLPHVPLNVIQRDLARTGCVDLTITNLLEGAVAFMPEDVTEGSQSPPAPSAPKF
	HP	PSSGPVTPQPTALTFAKSSWARQESLQERKQALYEYARRRFTERRAQEAD
		**** ***********
	MM	PSSGLATPQPTALTFAKSSWARQESLQERKQALYEYARRFRERQAQEAE
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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA131932) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03091> (SEQ ID NOS: 34, 44, and 54)

Determination of the whole base sequence of the cDNA insert of clone HP03091 obtained from cDNA library of human liver revealed the structure consisting of a 16-bp 5'-untranslated region, a 1452-bp ORF, and a 184-bp 3'-untranslated region. The ORF encodes a protein consisting of 483 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 14 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from leucine at position 34.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human OS-9 protein (SWISS-PROT Accession No. Q13438). Table 11 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the human OS-9 protein (OS). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 27.8% in the N-terminal region of 281 amino acid residues. The positions of eight cysteines were conserved between the two proteins.

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#### Table 11

HP MEEGGGGVRSLVPGGPVLLVLCGLLEASGGGRALPQLSDDIPFRVNWPGTEFSLPTTGVL MAAETILSSILGIILI-GILIPASLTGGVGSLNLEELSEMRYGIEILPLPVMGGQ 5 HP YKEDNYVIMTTAHKEKYKCILP---LVTSGDEEEEKDYKGPNPRELLEPLFKQSSCSYR .. \*\*\*. .\*.\*\*. .\*\*\*.\*. ....\* . .... \*\*... .\*..\* \*\* OS SOSSDVVIVSSKYKQRYECRLPAGAIHFQREREEETPAYQGPGIPELLSPM-RDAPCLLK HP IESYWTYEVCHGKHIROYHEEKETGQKINIHEYYLGNMLAKNLLFEKEREAEEKEKSNEI ...\*\*\*\* \*.\*.\*\*\* \* ... \* ... \*\*\* 10 OS TKDWWTYEFCYGRHIQQYHME-DSEIKGEV--LYLG-----YYQSAFD-----WDDET HP PTKNIEGQMTPYYPVGMGNGTPCSLKQNRPRSSTVMYIC---HPESKHEILSVAEVTTCE .. . . ....\*.. . \*\*\*. \*.\* ..\*\*\*...\* \* . \* .\*.\* .\*. OS AKASKQHRLKRYHSQTYGNGSKCDL-NGRPREAEVRFLCDEGAGISGDYIDRVDEPLSCS HP YEVVILTPLLCSHPKYRFRASPV-NDIFCQ-SLPGSPFKPLTLRQLEQQEEILRVPFRRN 15 \* ..\* \*\* \*\*.\*\* \* ..\*.. ..\*. \*\*. . ... . \*\* . .. OS YVLTIRTPRLCPHPLLRPPPSAAPQAILCHPSLQPEEYMAYVQRQADSKQYGDKIIEELQ

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA313678) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03092> (SEQ ID NOS: 35, 45, and 55)

Determination of the whole base sequence of the cDNA insert of clone HP03092 obtained from cDNA library of human liver revealed the structure consisting of a 19-bp 5'-untranslated region, a 1824-bp ORF, and a 269-bp 3'-untranslated region. The ORF encodes a protein consisting of

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607 amino acid residues and there existed at least six putative transmembrane domains. Figure 15 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the rat liver-specific transport protein (GenBank Accession No. L27651). Table 12 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the rat liver-specific transport protein (RN). Therein, the marks of - and \* represent a gap and an amino acid residue identical with that of the protein of the present invention, respectively. The both proteins shared a homology of 70.0% in the entire region.

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# Table 12

	HP	MGFEELLEQVGGFGPFQLRNVALLALPRVLLPLHFLLPIFLAAVPAHRCALPGAPANFSH
		**** ** ******** * **** **** * ***** * *
5	RN	${\tt MGFEDLLDKVGGFGPFQLRNLVLMALPRMLLPMHFILPVFMAAVPAHHCALPGAPANLSH}$
	HP	QDVWLEAHLPREPDGTLSSCLRFAYPQALPNTTLGEERQSRGELEDEPATVPCSQGWEYD
		** ******* ** ******* ** ** ** * * * * *
	RN	QDLWLEAHLPRETDGSFSSCLRFAYPQTVPNVTLGTEVSNSGEPEGEPLTVPCSQGWEYD
	HP	HSEFSSTIATESQVGIYIIHLEVECRWRQSPWEAAGRGLPWEEAEAAGLGRDKVSYSPSW
10		****
	RN	RSEFSSTIAT
	HP	RESLGGLLSGMEWDLVCEQKGLNRAASTFFFAGVLVGAVAFGYLSDRFGRRRLLLVAYVS
		***** * *** ** ****** *******
	RN	EWDLVCQQRGLNKITSTCFFIGVLVGAVVYGYLSDRFGRRRLLLVAYVS
15	HP	TLVLGLASAASVSYVMFAITRTLTGSALAGFTIIVMPLELEWLDVEHRTVAGVLSSTFWT
		**** **** * ** * ********* ********
	RN	SLVLGLMSAASINYIMFVVTRTLTGSALAGFTIIVLPLELEWLDVEHRTVAGVISTVFWS
	HP	GGVMLLALVGYLIRDWRWLLLAVTLPCAPGILSLWWVPESARWLLTQGHVKEAHRYLLHC
		*** ****** ***** ***** *** *** * ******
20		GGVLLLALVGYLIRSWRWLLLAATLPCVPGIISIWWVPESARWLLTQGRVEEAKKYLLSC
	HP	ARLNGRPVCEDSFSQEAVSKVAAGERVVRRPSYLDLFRTPRLRHISLCCVVVWFGVNFSY
		* ***** * * **** * ** ****** * ******
		AKLNGRPVGEGSLSQEALNNVVTMERALQRPSYLDLFRTSQLRHISLCCMMVWFGVNFSY
	HP	YGLSLDVSGLGLNVYQTQLLFGAVELPSKLLVYLSVRYAGRRLTQAGTLLGTALAFGTRL
<b>25</b>		*** *************
		YGLTLDVSGLGLNVYQTQLLFGAVELPSKIMVYFLVRRLGRRLTEAGMLLGAALTFGTSL
	HP	LVSSDMKSWSTVLAVMGKAFSEAAFTTAYLFTSELYPTVLRQTGMGLTALVGRLGGSLAP
		*** *** * * * *************
		LVSLETKSWITALVVVGKAFSEAAFTTAYLFTSELYPTVLRQTGLGLTALMGRLGASLAR
30	HP	LAALLDGVWLSLPKLTYGGIALLAAGTALLLPETRQAQLPETIQDVERKSAPTSLQEEEM
		********* *** **** ** ****** * *****
	RN	LAALLDGVWLLLPKVAYGGIALVAACTALLLPETKKAQLPETIQDVERKSTQEE
	HP	PMKQVQN
25	RN	DV

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AI016020) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

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<HP03116> (SEQ ID NOS: 36, 46, and 56)

Determination of the whole base sequence of the cDNA insert of clone HP03116 obtained from cDNA library of human epidermoid carcinoma cell line KB revealed the structure consisting of a 32-bp 5'-untranslated region, a 945-bp ORF, and a 110-bp 3'-untranslated region. The ORF encodes a protein consisting of 314 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 16 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. Application of the (-3,-1) rule, a method predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from lysine at position 20. In addition, there exist in the amino acid sequence of this protein three sites at which Nglycosylation may occur (Asn-Arg-Thr at position 167, Asn-Asn-Ser at position 200 and Asn-Ile-Ser at position 273).

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human Prostasin (SWISS-PROT Accession No. Q16651). Table 13 shows the comparison between amino acid sequences of the human protein of the present

invention (HP) and the human Prostasin (PR). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 39.8% in the entire region.

## Table 13

MGARGALLLALLLARAGLRKPESQEAAPLSGPCGRRVITSRIVGGEDAELGRWPW 10 HP ..\*.\* . .\* \*\* ... \*. ..\*\*\* . .\*\*.\*\* \*.\*\*\* PR MAQKGVLGPGQLGAVAILLYLGLLRSGTG-AEGAEAPCG-VAPQARITGGSSAVAGQWPW HP QGSLRLWDSHVCGVSLLSHRWALTAAHCFETYSDLSDPSGWMVQFGQLTSMPSFWSLQAY . \*\*\*\* \*\*.\*.\*.\*.\* .. . ... \*..\*. PR QVSITYEGVHVCGGSLVSEQWVLSAAHCF---PSEHHKEAYEVKLGA-HQLDSY---SED 15 HP YTRYFVSNIYLSPRYLGNSPY-DIALVKLSAPVTYTKHIQPICLQASTFEFENRTDCWVT \*.\*\* ... \*\*\*\*..\*\* \*.\*....\* \* \* .\* \* .\* \* PR AKVSTLKDIIPHPSYLQEGSQGDIALLQLSRPITFSRYIRPICLPAANASFPNGLHCTVT HP GWGYIKEDEALPSPHTLQEVQVAIINNSMCNHLF-LKYSFRKDIF--GDMVCAGNAQGGK 20 PR GWGHVAPSVSLLTPKPLQQLEVPLISRETCNCLYNIDAKPEEPHFVQEDMVCAGYVEGGK HP DACFGDSGGPLACNKNGLWYQIGVVSWGVGCGRPNRPGVYTNISHHFEWIQKLMAQSGMS PR DACQGDSGGPLSCPVEGLWYLTGIVSWGDACGARNRPGVYTLASSYASWIQSKVTELQPR HP QPDPSWPLLFFPLLWALPLLGPV 25 PR VVPQTQESQPDSNLCGSHLAFSSAPAQGLLRPILFLPLGLALGLLSPWLSEH

30 Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA159101) among ESTs. However, since they are partial sequences, it can not be judged whether or

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not they encode the same protein as the protein of the present invention.

# <HP10618> (SEQ ID NOS: 37, 47, and 57)

Determination of the whole base sequence of the cDNA insert of clone HP10618 obtained from cDNA library of human fibrosarcoma cell line HT-1080 revealed the structure consisting of a 215-bp 5'-untranslated region, a 285-bp ORF, and a 1194-bp 3'-untranslated region. The ORF encodes a protein consisting of 94 amino acid residues and there existed a putative transmembrane domain at the N-terminus. Figure 17 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 10 kDa that was almost identical with the molecular weight of 9,709 predicted from the ORF.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA287125) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

# 25 <HP10619> (SEQ ID NOS: 38, 48, and 58)

Determination of the whole base sequence of the cDNA insert of clone HP10619 obtained from cDNA library of the human fibrosarcoma cell line HT-1080 revealed the structure consisting of a 11-bp 5'-untranslated region, a 657-bp ORF, and a 854-bp 3'-untranslated region. The ORF encodes a protein consisting of 218 amino acid residues and there existed a putative transmembrane domain at the N-terminus.

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Figure 18 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. Z43089) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

# <HP10622> (SEQ ID NOS: 39, 49, and 59)

Determination of the whole base sequence of the cDNA insert of clone HP10622 obtained from cDNA library of the human liver revealed the structure consisting of a 43-bp 5'untranslated region, a 1383-bp ORF, and a 165-bp 3'untranslated region. The ORF encodes a protein consisting of amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 19 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from serine at position 17. addition, there exist in the amino acid sequence of this protein four sites at which N-glycosylation may occur (Asn-Ser-Ser at position 23, Asn-Met-Ser at position 115, Asn-Glu-Thr at position 296 and Asn-Tyr-Thr at position 357).

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human angiopoietin-1 (GenBank

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Accession No. U83508). Table 14 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the human angiopoietin-1 (AN). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 28.2% in the entire region and a homology of 39.1% in the C-terminal region of 215 amino acid residues.

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#### Table 14

**MFTIKLLLFIVPLVISS** HP AN MTVFLSFAFLAAILTHIGCSNQRRSPENSGRRYNRIQHGQCAYTFILPEHDGNCRESTTD 5 HP RIDQDNSSFDSLSPEPKSRFAMLDDVKILANGLLQLGHGLKDF-VHKTKGQINDIFQKLN AN QYNTNALQRDAPHVEPDFSSQKLQHLEHVMENYTQWLQKLENYIVENMKSEMAQI-QQNA HP IFDQSFYDLSLQTSEIKEEEKELRR-TTYKLQVKNEEVKNMSLELNSKLESLLEEKILLQ . ... \*.. \*\* ..... \*. \*. . . \*\* \*.. . 10 AN VONHTATMLEIGTSLLSQTAEQTRKLTDVETQVLNQTSRLEIQLLENSLSTYKLEKQLLQ HP QKVKYLE-EQLTNLIQNQPETPEHPEVTSLKTFVEKQDNSIKDLLQTVEDQYKQLNQQHS \*. . \*. .. ..\*... . \* . ...\*. \* ...\* ...\*. . ...\* . AN QTNEILKIHEKNSLLEHKILEMEGKHKEELDTLKEEKEN-LQGLVTRQTYIIQELEKQLN HP QIKEIENQLRRTSIQEPTEISLSSKPRAPRTTPFLQLNEIRNVKHDGIPAECTTIYNRGE 15 AN RATTNNSVLQKQQL-ELMDTVHNLVNLCTKEGVLL--KGGKREEEKPFR-DCADVYQAGF HP HTSGMYAIRPSN-SQVFHVYCDV-ISGSPWTLIQHRIDGSQNFNETWENYKYGFGRLDGE ..\*\*.\*. .\* .. .\*.\*. .\*. \*\*.\*\* \*\*\* .\*. .\*. \*\*\* \*\*\* .\*. AN NKSGIYTIYINNMPEPKKVFCNMDVNGGGWTVIQHREDGSLDFQRGWKEYKMGFGNPSGE 20 HP FWLGLEKIYSIVKQSNYVLRIELEDWKDNKHYIEY-SFYLGNHETNYTLHLVAITGNVPN AN YWLGNEFIFAITSQRQYMLRIELMDWEGNRAYSQYDRFHIGNEKQNYRLYLKGHTGTAGK HP AIP-ENKDLVFSTWDHKAKGHF-NCPEGYSGGWWWHDECGENNLNGKYNKPRAKSKPERR 25 AN OSSLILHGADFSTKDADNDNCMCKCALMLTGGWWF-DACGPSNLNGMFY--TAGQNHGKL HP RGLSWKSQNGRLYSIKSTKMLIHPTDSESFE .\*..\*. .\*. \*\*..\*\*.\*.\* \* AN NGIKWHYFKGPSYSLRSTTMMIRPLDF

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for

example, Accession No. R86161) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

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# <HP10625> (SEQ ID NOS: 40, 50, and 60)

Determination of the whole base sequence of the cDNA insert of clone HP10625 obtained from cDNA library of the human liver revealed the structure consisting of a 133-bp 5'-untranslated region, a 651-bp ORF, and a 465-bp 3'-untranslated region. The ORF encodes a protein consisting of 216 amino acid residues and there existed two putative transmembrane domains. Figure 20 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. R59052) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP02883> (SEQ ID NOS: 61, 71, and 81)

Determination of the whole base sequence of the cDNA insert of clone HP02883 obtained from cDNA library of human epidermoid carcinoma cell line KB revealed the structure consisting of a 191-bp 5'-untranslated region, a 1179-bp ORF, and a 2657-bp 3'-untranslated region. The ORF encodes a protein consisting of 392 amino acid residues and there existed three putative transmembrane domains. Figure 21 depicts the hydrophobicity/hydrophilicity profile, obtained

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by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 40 kDa that was almost identical with the molecular weight of 43,381 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the Caenorhabditis elegans the similar to was (GenBank Accession CET24F1.2 hypothetical protein Z49912). Table 15 shows the comparison between amino acid sequences of the human protein of the present invention (HP) hypothetical protein Caenorhabditis elegans and the CET24F1.2 (CE). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 35.4% in the N-terminal region of 178 amino acid residues.

#### Table 15

HP NRNCWDCPHCEQYNGFQENGDYNKPIPAQYLEHLNHVVSSAPSLRDP-SQPQX .**** ****** * .***** *		
MEVAAAVGVIASVPILYK-AIRPR-IKTSVECWFCRKSTKVEY( HP NRNCWDCPHCEQYNGFQENGDYNKPIPAQYLEHLNHVVSSAPSLRDP-SQPQX .**** ****** *.***** * * *	HP	MEGVSALLARCPTAGLAGGLGVTACAAAGVLLYRIARRMKPTHTMVNCWFCNQDTLVPYG
HP NRNCWDCPHCEQYNGFQENGDYNKPIPAQYLEHLNHVVSSAPSLRDP-SQPQX .**** ****** * .***** *		** *** * * * * * * * * * *
CE QRNSFTCPSCEQYNGFTEDGDYNRRIPGQAWTTPKRYCEPGKMQSEKPSTFLDRFGGVNN HP WVSSQVLLCKRCNHHQTTKIKQLAAFAPREEGRYDEEVEVYRHHLEQMYKLCRPCQAAVI	CE	MEVAAAVGVIASVPILYK-AIRPR-IKTSVECWFCRKSTKVEYQ
CE QRNSFTCPSCEQYNGFTEDGDYNRRIPGQAWTTPKRYCEPGKMQSEKPSTFLDRFGGVNN HP WVSSQVLLCKRCNHHQTTKIKQLAAFAPREEGRYDEEVEVYRHHLEQMYKLCRPCQAAVI ** ** *** ** ** ** ** ** ** ** **	HP	NRNCWDCPHCEQYNGFQENGDYNKPIPAQYLEHLNHVVSSAPSLRDP-SQPQQ
HP WVSSQVILCKRCNHHQTTKIKQLAAFAPREEGRYDEEVEVYRHHLEQMYKLCRPCQAAVI **.** **.*.*.*.**.**.**.**.**.**		***** ****** *.****** * * *
CE SPKASNGLCSECNLGQEIIMNKVAEFEPIDEDRWNEELEDYRYKLERMYQLCPRCTIQVI HP YYIKHQNRQLRALLLSHQFKRREADQTHAQNFSSAVKSPVQVILLRALAFLACAFLLTTI	CE	QRNSFTCPSCEQYNGFTEDGDYNRRIPGQAWTTPKRYCEPGKMQSEKPSTFLDRFGGVNM
CE SPKASNGLCSECNLGQEIIMNKVAEFEPIDEDRWNEELEDYRYKLERMYQLCPRCTIQVI HP YYIKHQNRQLRALLLSHQFKRREADQTHAQNFSSAVKSPVQVILLRALAFLACAFLLTTA	HP	WVSSQVLLCKRCNHHQTTKIKQLAAFAPREEGRYDEEVEVYRHHLEQMYKLCRPCQAAVE
HP YYIKHQNRQLRALLLSHQFKRREADQTHAQNFSSAVKSPVQVILLRALAFLACAFLLTTA		** ** ** **.* .*. * **. **. **.
***	CE	SPKASNGLCSECNLGQEIIMNKVAEFEPIDEDRWNEELEDYRYKLERMYQLCPRCTIQVH
	HP	YYIKHQNRQLRALLLSHQFKRREADQTHAQNFSSAVKSPVQVILLRALAFLACAFLLTTA
CE GKLEEDKKKY-SYLLKVKYKLKHAIGSTLREVMNNQKRSRRFFFAGGSTCEALHFGCLIS		***
	CE	GKLEEDKKKY-SYLLKVKYKLKHAIGSTLREVMNNQKRSRRFFFAGGSTCEALHFGCLIS

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. F11409) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

# 10 <HP03140> (SEQ ID NOS: 62, 72, and 82)

Determination of the whole base sequence of the cDNA insert of clone HP03140 obtained from cDNA library of human fibrosarcoma cell line HT-1080 revealed the structure consisting of a 29-bp 5'-untranslated region, a 1494-bp ORF, and a 972-bp 3'-untranslated region. The ORF encodes a protein consisting of 497 amino acid residues and there existed one putative transmembrane domain. Figure 22 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 51 kDa that was almost identical with the molecular weight of 54,245 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein similar to the Caenorhabditis elegans protein hypothetical CELC50D2 (GenBank Accession AF040642). Table 16 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the Caenorhabditis elegans hypothetical protein CELC50D2 (CE). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that

of the protein of the present invention, respectively. The both proteins shared a homology of 37.9% in the N-terminal region of 393 amino acid residues.

5 Table 16

	HP	MALWRGSAYAGFLALAVGCVFLLEPELPGSALRSLWSSLCLGPAPAPPGPVSPEGRLAAA
		* *
	CE	MFSETFVPSIFSYKHRLLHLSVLFFIVPYWYSYYNDQHRLSSYSVETAMFLS
10	HP	WDALIVRPVRRWRRVAVGVNACVDVVLSGVKLLQALGLSPGNGKDHSILHSRNDLEEAFI
		*. **.* * * ********
	CE	WERAIVKPGAMFKKAVIGFNCNVDLIVSGVRVVDALNTTCSEGKDQETLETLADLHQTFA
	HP	HFMWKGAAAERFFSDKETFHDIAQVASEFPGAQHYVGGNAALIGQKFAAN-SDLKVLLCG
		*** ****** * * * * * * * * * * * * * * *
15	CE	HFFQRGAAAERYMSSEDQFNLLVAESEASTRSHHHIGGNAALMADRIAANFPSTEVYLVG
	HP	PVGPRLHELLDDNVFVPPESLQEVDEFHLILEYQAGEEWGQLKAPHANRFIFSHDLSNGA
		*.***** .*
	CE	PIGPRSQALLHPSVKRTNSTRILKDELHVILEYKQGEILGDWVAPSSSRFITSHDHFSGS
	HP	MNMLEVFVSSLEEFQPDLVVLSGLHMMEGQSKELQRKRLLEVVTSISDIPTGIPVHLELA
20		**.**.****** *****
	CE	MVVMEMFFKAIAQFRPDLVVITGVHLLEFQSKEMRQEKMRLIKRNLLQIPPKVPIHLELG
	HP	SMTNRELMSSIVHQQVFPAVTSLGLNEQELLFLTQSASGPH-SSLSSWNGVPDVGMVSDI
		* **. * * * * * *
	CE	SLAD-EIFSTDVINKILPYVDSLGINEQELTFLSHIANGPHMEEYPVQAGTVHVHKVVEM
25	HP	LFWILKEHGRSKSRASDLTRIHFHTLVYHILATVDGHWANQLAAVAAGARVAGT
		* * * * * * * * * * * * * * * * * * * *
	CE	LHWLLKTYGRDPTGQIASKTGYRLSRIHFHCLTYHIMVSSGTDWSNLAAGLAAGARIAGR
	HP	QACATETIDTSRVSLRAPQEFMTSHSEAGSRIVLNPNKPVVEWHREGISFHFTPVLVC
		.**.* *.*.
30	CE	LSCNIGANTMDSELLEIRTPANFVLDKKIEKNYQFEAHKYMLTPFNIARCSTRLIRRKPP
	HP	KDPIRTVGLGDAISAEGLFYSEVHPHY
	CE	GGGILDEGVTFSDVHNVILNPTTRLPYPEEQLREHIEKTSSEIMKERNKIRYGTRKKKDS

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA356000) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

## <HP10628> (SEQ ID NOS: 63, 73, and 83)

Determination of the whole base sequence of the cDNA insert of clone HP10628 obtained from cDNA library of human fibrosarcoma cell line HT-1080 revealed the structure consisting of a 66-bp 5'-untranslated region, a 1254-bp ORF, and a 297-bp 3'-untranslated region. The ORF encodes a protein consisting of 417 amino acid residues and there existed four putative transmembrane domains. Figure 23 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 46 kDa that was almost identical with the molecular weight of 45,461 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the Schistosoma mansoni ATP-cassette family protein (GenBank Accession No. L26286). Table 17 shows the comparison between amino acid sequences of the protein of the present invention (HP) Schistosoma mansoni ATP-cassette family protein Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The

both proteins shared a homology of 39.5% in the C-terminal region of 294 amino acid residues.

#### Table 17

5 HP MLVHLFRVGIRGGPFPGRLLPPLRFQTFSAVRYSDGYRSSSLLRAVAHLRSQLWAHLPRA MFSALCRRGFLTNKVSQFRSTYKCDHYNLKT HP PLAPRWSPSAWCWVGGALLGPMVLSKHPHLCLVALCEAEEAPPASSTPHVVGSRFNWKLF SM HIKPLKCSSSLRLTVGTGLFIALHSKISPESRIQTVQCEVDSYQTDQITFAKSGGIPRYI HP WQFLHPHLLVLGVAVVLALGAALVNVQIPLLLGQLVEVVAKYTRDHVGSFMTESQNLSTH 10 .. \*. . \* \*.. \*. \*\*..\*\* \*\*\* \*\*..\*. .... .\* \* \*... SM GVLILPDCVYLFGAILGAFVAAVMNVYIPLYLGDFVSSLSRCVVTHEG-FVSAVYVPTLR HP LLILYGVQGLLTFGYLVLLSHVGERMAVDMRRALFSSLLRYCQPQGAELGQDITFFDANK \* .\*.\* \*\* \*. \*\*. \*\*\*\*\* \*\* .\*\*..\*. \* SM LCSSYLLOSLSTFLYIGLLGSVGERMARRMRIQLFRKLV-Y-----QDVAYFDVHS 15 HP TGQLVSRLTTDVQEFKSSFKLVISQGLRSCTQVAGCLVSLSMLSTRLTLLLLMVATPALMG SM SGKLVEIIGSDVONFKSSFKOCISOGLRNGIQVVGSVFALLSISPTLTAALIGCLPCVFL HP VGTLMGSGLRKLSCQCQEQIARAMGVADEALGNVRTVRAFAMEQREEERYGAELEACRCR \*\*\*\*\*\*\*\*\*\* 20 SM IGSLMGTELRHISREVQSQNSLFASLIDEAFSHIRTVKSLAMEDFLINKINYNVDKAKML HP AEELGRGIALFQGLSNIAFNCMVLGTLFIGGSLVAGQQLTGGDLMSFLVASQTVQRL SM SEKLSFGIGSFQGLSNLTLNGVVLGVLYVGGHLMSRGELDAGHLMSFLATTQTLQRSLTQ 25

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. U66688) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

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<HP10629> (SEQ ID NOS: 64, 74, and 84)

Determination of the whole base sequence of the cDNA insert of clone HP10629 obtained from cDNA library of human retinoblastoma cell line WERI-RB revealed the structure consisting of a 259-bp 5'-untranslated region, a 1950-bp ORF, and a 1060-bp 3'-untranslated region. The ORF encodes a protein consisting of 649 amino acid residues and there existed at least eight putative transmembrane domains. Figure 24 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein data base using the amino acid sequence of the present protein revealed that the was similar to the Caenorhabditis elegans hypothetical protein CELF38B6 (GenBank Accession No. U40060). Table 18 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the Caenorhabditis elegans hypothetical protein CELF38B6 (CE). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 39.1% in the C-terminal region of 445 amino acid residues.

# Table 18

	HP	${\tt MIPNQHNAGAGSHQPAVFRMAVLDTDLDHILPSSVLPPFWAKLVVGSVAIVCFARSYDGD}$
	CE	MKYAEINVNSGKHFRLNYKLHETS
5	HP	FVFDDSEAIVNNKVAGVVGRADLLCALFFLLSFLGYCKAFRESNKEGAHSSTFWVLLSIF
	CE	TLGYHVVNIICHTVATLVFYKLGKQLEHIFDFFNIAFSASILFAVHPVHTEAVANITGRA
	HP	${\tt LGAVAMLCKEQGITVLGLNAVFDILVIGKFNVLEIVQKVLHKDKSLENLGMLRNGGLLFR}$
	CE	ELIMTIFSLAALILHVKNREINCKFVLLVILSTLSKEQGLMTIPIAICIDFLAHRSCRSN
	HP	MTLLTSGGAGMLYVRWRIMGTGPPAFTEVDNPASFADSMLVRAVNYNYYYSLNAWLLLCP
10		* * ****** .* . * .**.**.**
	CE	FVRMICLLVAIGFLRMMVNGFEAAKFTKLDNPTAFLNSKFYRMINYTYIWLYHAYLLVIP
	HP	wwlcfdwsmgcipliksisdwrvialaalwfcliglicqalcsedghkrriltlglgflv
		****.****. * * . ** * . * . * .
	CE	VNLCFDYSMGCISSITTMWDLRALSPVLIFTIVIIGVKFQNECRAFTLSSLMGI
15	HP	IPFLPASNLFFRVGFVVAERVLYLPSIGYCVLLTFGFGALSKHTKKKKLIAAVVLGILFI
		*.********* *** .******* *.*. * ** * *
	CE	ISFLPASNIFFTVGFSIAERVLYLPSAGFCLLCAIIFKKLSVHFKNADVLSITLILLLIS
	HP	NTLRCVLRSGEWRSEEQLFRSALSVCPLNAKVHYNIGKNLADKGNQTAAIRYYREAVRLN
		* * *****.* **.***** ***.** *.*.** . **.
20	CE	KTYRRSGEWKTELSLYSSGLSVCPTNAKIHYNLGKVLGDNGLTKDAEKNYWNAIKLD
	HP	PKYVHAMNNLGNILKERNELQEAEELLSLAVQIQPDFAAAWMNLGIVQNSLKRFEAAEQS
		*.* .*.**** *
	CE	PSYEQALMNLGNLLEKSGDSKTAESLLARAVTLRPSFAVAWMNLGISQMNLKKYYEAEKS
	HP	YRTAIKHRRKYPDCYYNLGRLYADLNRHVDALNAWRNATVLKPEHSLAWNNMIILLDNTG
25		** .** *** **. **. *****.** .*.*
	CE	LKNSLLIRPNSAHCLFNLGVLYQRTNRDEMAMSAWKNATRIDPSHSQSWTNLFVVLDHLS
	HP	NLAQAEAVGREALELIPNDHSLMFSLANVLGKSQKYKESEALFLKAIKANPNAASYHGNL
		*****
	CE	QCSQVIDLSYQALSSVPNESRVHMQIGSCHAKHSNFTAAENHIKSAIDLNPTSVLFHANL
30	HP	AVLYHRWGHLDLAKKHYEISLQLDPTASGTKENYGLLRRKLELMQKKAV
		**.* ** * *.***.*
	CE	GILYORMSRHKEAESQYRIVLALDSKNIVAKQNLQKLEEHNCYNSTLP

Furthermore, the search of the GenBank using the base

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sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA450191) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

## <HP10635> (SEQ ID NOS: 65, 75, and 85)

Determination of the whole base sequence of the cDNA insert of clone HP10635 obtained from cDNA library of human retinoblastoma cell line WERI-RB revealed the structure consisting of a 65-bp 5'-untranslated region, a 282-bp ORF, and a 111-bp 3'-untranslated region. The ORF encodes a protein consisting of 93 amino acid residues and there existed two putative transmembrane domains. Figure 25 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 10 kDa that was almost identical with the molecular weight of 9,489 predicted from the ORF.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA516481) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

### <HP10636> (SEQ ID NOS: 66, 76, and 86)

Determination of the whole base sequence of the cDNA insert of clone HP10636 obtained from cDNA library of human fibrosarcoma cell line HT-1080 revealed the structure

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consisting of a 179-bp 5'-untranslated region, a 1278-bp ORF, and a 255-bp 3'-untranslated region. The ORF encodes a protein consisting of 425 amino acid residues and there existed ten putative transmembrane domains. Figure 26 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. Z43270) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

### <HP10640> (SEQ ID NOS: 67, 77, and 87)

Determination of the whole base sequence of the cDNA insert of clone HP10640 obtained from cDNA library of human retinoblastoma cell line WERI-RB revealed the structure consisting of a 52-bp 5'-untranslated region, a 450-bp ORF, and a 553-bp 3'-untranslated region. The ORF encodes a protein consisting of 149 amino acid residues and there existed at least two putative transmembrane domains. Figure 27 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 17 kDa that was almost identical with the molecular weight of 16,829 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the Arabidopsis thaliana hypothetical

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protein F27F23.14 (GenBank Accession No. AC003058). Table 19 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the Arabidopsis thaliana hypothetical protein F27F23.14 (AT). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 46.5% in the entire region other than the N-terminal region.

## Table 19

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. N34717) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10644> (SEQ ID NOS: 68, 78, and 88)

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Determination of the whole base sequence of the cDNA insert of clone HP10644 obtained from cDNA library of the human retinoblastoma cell line WERI-RB revealed the structure consisting of a 221-bp 5'-untranslated region, a 1191-bp ORF, and a 204-bp 3'-untranslated region. The ORF encodes a protein consisting of 396 amino acid residues and there existed two putative transmembrane domains. Figure 28 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein.

The search of the protein data base using the amino acid sequence of the present protein revealed that the the Caenorhabiditis elegans was similar to protein hypothetical B0511.8 (GenBank Accession No. protein AF067608). Table 20 shows the comparison between amino acid sequences of the human protein of the present invention (HS) and the Caenorhabiditis elegans hypothetical protein B0511.8 (CE). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 31.3% in the region of 361 amino acid residues other than the N-terminal region and the C-terminal region.

## Table 20

	HS	MAMIELGFGRONFHPLKRKSSLLLKL
	CE	CDKNGQYLSVQEEIDAENKVQRKIAPGLNEKVLERVTQMLMKQEKSTETYMIWLKNLRVP
5	HS	IAVVFAVLLFCEFLIYYLAIFQCNWPEVKTTASDGEQTTREPVLKAMFLADTHLLGEFLG
		* * * * . * . * . * . * . *
	CE	ILLAIILVVYNEYFIFFIAFSSCQWPCKYGRCS-ESSVKAFMISDTHLLGKING
	HS	${\tt HWLDKLRREWQMERAFQTALWILLQPEVVFILGDIFDEGKWSTPEAWADDVERFQKMFRHP}$
		****** ****** *. *.*.*****
10	CE	HWLDKLKREWQMYQSFWISTWIHSPDVTFFLGDLMDEGKWAGRPVFEAYAERFKKLFG
	HS	SHVQLKVVAGNHDIGFHYEMNTYKVERFEKVFSSERLFSWKGINFVMVNSVALNGDGCGI
	CE	DNEKVITLAGNHDLGFHYALVQTFATHLTPTVELKNYLLIMPETLEMFKKEFRR
	HS	CSETEAELIEVSHRLNCSREARG-SSR-CGPGPLLPTSAPVLLQHYPLYRRS
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	CE	GLIDEMKIKKHRFVLINSMAMHGDGCRLCHEAELILEKIKSRNPKNRPIVLQHFPLYRKS
	HS	DANCSGEDAAPAEERDIPFKENYDVLSREASQKLLWWLQPRLVLSGHTHSACEVH
		**.*. * * *.*. * *.*. *
	CE	DAECDQVDEQHEIDLKEMYREQWDTLSKESSLQIIDSLNPKAVFGGHTHKMCKKKWNKTG
20	HS	HGGRVPELSVPSFSWRNRNNPSFIMGSITPTDYTLSKCYLPREDVVLIIYC-GVVGFLVV
		* * * ***** . *
	CE	NSEYFYEYTVNSFSWRNGDVPAMLLVVIDGDNVLVSSCRLPSEILQIMVYIFGGIGILAK
	HS	LTLTHFGLLASPFLSGLNLLGKRKTR
		•
<b>25</b>	CE	MYNDLITPAPLEWNVNNIAVCTAIILVMIINVVALIFTIFWCLRSKDEGGEIDSNGVVIN

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. R88381) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

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<HP10656> (SEQ ID NOS: 69, 79, and 89)

Determination of the whole base sequence of the cDNA insert of clone HP10656 obtained from cDNA library of the line U937 revealed the structure lymphoma cell consisting of a 68-bp 5'-untranslated region, a 1053-bp ORF, The ORF encodes a and a 739-bp 3'-untranslated region. protein consisting of 350 amino acid residues and there existed two putative transmembrane domains. Figure depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 41 kDa that was almost identical with the molecular weight of 40,043 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 54 kDa to which sugar chains are presumably there exist in the amino acid attached. In addition, sequence of this protein four sites at which N-glycosylation may occur (Asn-Cys-Thr at position 148, Asn-Tyr-Thr at position 155, Asn-Gln-Thr at position 162 and Asn-Lys-Ser at position 190).

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA917816) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

30 <HP10672> (SEQ ID NOS: 70, 80, and 90)

Determination of the whole base sequence of the cDNA insert of clone HP10672 obtained from cDNA library of the

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human thymus revealed the structure consisting of a 244-bp 5'-untranslated region, a 462-bp ORF, and a 77-bp 3'-untranslated region. The ORF encodes a protein consisting of 153 amino acid residues and there existed a putative secretory signal at the N-terminus and one putative transmembrane domain at the C-terminus. Figure 30 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. When expressed in COS cells, a product of 17 kDa was observed in the membrane fraction.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. N48700) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03194> (SEQ ID NOS: 91, 101, and 111)

Determination of the whole base sequence of the cDNA insert of clone HP03194 obtained from cDNA library of human epidermoid carcinoma cell line KB revealed the structure consisting of a 120-bp 5'-untranslated region, a 912-bp ORF, and a 2406-bp 3'-untranslated region. The ORF encodes a protein consisting of 303 amino acid residues and there existed four putative transmembrane domains. Figure 31 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein data base using the amino acid sequence of the present protein revealed that the

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protein was similar to the mouse hyperpolarization-activated cation channel HAC3 (GenBank Accession No. AJ225124). Table 21 shows the comparison between amino acid sequences of the human protein of the present invention (HS) and the mouse hyperpolarization-activated cation channel HAC3 (MM). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 92.5% in the N-terminal region of 293 amino acid residues.

#### Table 21

HS MEAEORPAAGASEGATPGLEAVPPVAPPPATAASGPIPKSGPEPKRRHLGTLLQPTVNKF 15 \*\*,\*,\*\*\*\*\*,\*,\*\*\*\*, \*, \*\*,\*\*, \* \*\*\*\* .\*,\*\*\*\*\*\* MM MEEEARPAAGAGEAATPARET-PPAAPAQARAASGGVPESAPEPKRRQLGTLLQPTVNKF HS SLRVFGSHKAVEIEQERVKSAGAWIIHPYSDFRFYWDLIMLLLMVGNLIVLPVGITFFKE \*\*\*\*\*\*\*\*\*\*\* MM SLRVFGSHKAVEIEQERVKSAGAWIIHPYSDFRFYWDLIMLLLMVGNLIVLPVGITFFKE 20 HS ENSPPWIVFNVLSDTFFLLDLVLNFRTGIVVEEGAEILLAPRAIRTRYLRTWFLVDLISS MM ENSPPWIVFNVLSDTFFLLDLVINFRTGIVVEEGAEILLAPRAIRTRYLRTWFLVDLISS HS IPVDYIFLVVELEPRLDAEVYKTARALRIVRFTKILSLIRLIRLSRLIRYIHQWEEIFHM 25 MM IPVDYIFLVVELEPRLDAEVYKTARALRIVRFTKILSLLRLLRLSRLIRYIHQWEEIFHM HS TYDLASAVVRIFNLIGMMLLLCHWDGCLQFLVPMLQDFPPDCWVSINHMVVRSPHSSAFP \*\*\*\*\*\*\*\*\*\*\*\*\*\* MM TYDLASAVVRIFNLIGMMLLLCHWDGCLQFLVPMLQDFPSDCWVSMNRMVNHSWGRQYSH HS GPS 30 MM ALFKAMSHMLCIGYGQQAPVGMPDVWLTMLSMIVGATCYAMFIGHATALIQSLDSSRRQY

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AI571225) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

# <HP03219> (SEQ ID NOS: 92, 102, and 112)

Determination of the whole base sequence of the cDNA insert of clone HP03219 obtained from cDNA library of human lymphoma cell line U937 revealed the structure consisting of a 55-bp 5'-untranslated region, a 852-bp ORF, and a 237-bp 3'-untranslated region. The ORF encodes a protein consisting of 283 amino acid residues and there existed four putative transmembrane domains. Figure 32 depicts hydrophobicity/hydrophilicity profile, obtained by the Kytemethod, of the present protein. translation resulted in formation of a translation product of high molecular weight.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human putative membrane protein 54TMp (GenBank Accession No. AF004876). Table 22 shows the comparison between amino acid sequences of the human protein of the present invention (HS) and the human putative membrane protein 54TMp (TM). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 56.5% in the entire region.

#### Table 22

MADPHOLFDDTSSAQSRGYGAQRAPGGLSYPAASPT-PHAAF HS .\*\*..\*\*\*\* 5 TM MAYHSGYGAHGSKHRARAAPDPPPLFDDT----SGGYSSQ--PGGYPATGADVAFSVNHL HS LADPVSNMAMAYGSSLAAQGKELVDKNIDRFIPITKLKYYFAVDTMYVGRKLGLLFFPYL \*.\*\*..\*.\*\*\*\*\* TM LGDPMANVAMAYGSSIASHGKDMVHKELHRFVSVSKLKYFFAVDTAYVAKKLGLLVFPYT HS HQDWEVQYQQDTPVAPRFDVNAPDLYIPAMAFITYVLVAGLALGTQDRFSPDLLGLQASS 10 TM HONWEVQYSRDAPLPPRQDLNAPDLYIPTKAFITYVLLAGMALGIQKRFSPEVLGLCAST HS ALAWLTLEVLAILLSLYLVTVNTDLTTIDLVAFLGYKYVGMIGGVLMGLLFGKIGYYLVL \*\*.\*...\*\*\*.\*\*.\*\*.\*\*..\*\*..\*...\*... TM ALVWVVMEVLALLLGLYLATVRSDLSTFHLLAYSGYKYVGMILSVLTGLLFGSDGYYVAL 15 HS GWCCVAIFVFMIRTLRLKILADAAAEGVPVRGARNQLRMYLTMAVAAAQPMLMYWLTFHL TM AWTSSALMYFIVRSLRTAAL-GPDSMGGPV--PRQRLQLYLTLGAAAFQPLIIYWLTFHL HS VR 20 \*\* TM VR

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. H86659) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03236> (SEQ ID NOS: 93, 103, and 113)

Determination of the whole base sequence of the cDNA insert of clone HP03236 obtained from cDNA library of human

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fibrosarcoma cell line HT-1080 revealed the structure consisting of a 252-bp 5'-untranslated region, a 1467-bp ORF, and a 620-bp 3'-untranslated region. The ORF encodes a protein consisting of 488 amino acid residues and there existed seven putative transmembrane domains. Figure 33 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the Caenorhabditis elegans hypothetical protein ZC513.5 (GenBank Accession No. U53155). Table 23 shows the comparison between amino acid sequences of the human protein of the present invention (HS) and the Caenorhabditis elegans hypothetical protein ZC513.5 (CE). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 39.5% in the intermediate region of 365 amino acid residues.

#### Table 23

HS MAGKGSSGRRPLLLGLLVAVATVHLVICPYTKVEESFNLQATHDLLYHWQDLEQYDHLEF .\*\*\* .\* MKMKYDHSQF CE 5 HS PGVVPRTFLGPVVIAVFSSPAVYVLSLLEMSKFYSQLIVRGVLGLGVIFGLWTLQKEVRR CE PGVVPRTFIGPISLAILSSPMSFIFRFWAIPKMWQLLLIRATLGLMNAMAFLYFARSVNR HS HFGAMVATMFCWVTAMQFHLMFYCTRTLPNVLALPVVLLALAAWLRHEWARFIWLSAFAI 10 CE KFGRETAMYLRLIMCTQFHYIFYMSRPLPNTFALILVMIVFERLLEGRYESAVRYATASV HS IVFRVELCLFLGLLLL--LALGNRKV-SVVRALRHAVPAGILCLGLTVAVDSYFWRQLTW CE ILFRCELVLLYGPIFLGYMISGRLKVFGFDGAIAIGVRIAAMCLAVSIPIDSYFWGRPLW HS PEGKVLWYNTVLNKSSNWGTSPLLWYFYSALPRGLGCSLLFIPLG-LVDRRTHAPTVLAL 15 CE PEGEVMFFNVVENRSHEYGTQPFLWYFYSALPRCLLTTTLLVPLGLLVDRRLPQIVLPSV HS GFMALYSLLPHKELRFIIYAFPMLNITAARGCSYLLNNYKKSWLYKAGSLLVIGHLVVNA CE IFIFLYSFLPHKELRFIIYVLPIFCLSAAVFCARMLINRHKSFFRMILFFGVILHLLANV 20 HS AYSATALYVSHFNYPGGVAMQ--RLHQLVPPQTDVLLHIDVAAAQTGVSRFLQVNSAWRY CE LCTGMFLLVASKNYPGFDALNYLQFQNRFDAKKPVTVYIDNACAQTGVNRFLHINDAWT

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA744858) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the

<HP03237> (SEQ ID NOS: 94, 104, and 114)

present invention.

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Determination of the whole base sequence of the cDNA insert of clone HP03237 obtained from cDNA library of human fibrosarcoma cell line HT-1080 revealed the structure consisting of a 101-bp 5'-untranslated region, a 549-bp ORF, and a 1106-bp 3'-untranslated region. The ORF encodes a protein consisting of 182 amino acid residues and there existed four putative transmembrane domains. Figure 34 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human intestinal membrane A4 protein (SWISS-PROT Accession No. Q04941). Table 24 shows the comparison between amino acid sequences of the human protein of the present invention (HS) and the human intestinal membrane A4 protein (IM). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 32.4% in the intermediate region of 111 amino acid residues.

# Table 24

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. R14227) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

#### <HP03267> (SEQ ID NOS: 95, 105, and 115)

Determination of the whole base sequence of the cDNA insert of clone HP03267 obtained from cDNA library of human liver revealed the structure consisting of a 148-bp 5'untranslated region, a 555-bp ORF, and a 715-bp untranslated region. The ORF encodes a protein consisting of 184 amino acid residues and there existed two putative 35 depicts Figure transmembrane domains. hydrophobicity/hydrophilicity profile, obtained by the Kyteof the present protein. Doolittle method, translation resulted in formation of a translation product of 21 kDa that was almost identical with the molecular

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weight of 20,733 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human polyposis locus protein 1 (SWISS-PROT Accession No. Q00765). Table 25 shows the comparison between amino acid sequences of the human protein of the present invention (HS) and the human polyposis locus protein 1 (PL). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 59.1% in the entire region.

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Table 25

PL MRERFDRFLHEKNCMTDLLAKLEAKTGVNRSFIALGVIGLVALYLVFGYGASLLCNL

PL IGFGYPAYISIKAIESPNKEDDTQWLTYWVVYGVFSIAEFFSDIFLSWFPFYYMLKCGFL

HS LFCMAPRPWNGALMLYQRVVRPLFLRHHGAVDRIMNDLSGRALDAAAGITRNVKPSQTPQ
\*.\*\*\*.\* \*\*\* .\*\*.\*\*.\*\*.\*\*.\*\*.\*\*.\*\*.\*\*

PL LWCMAPSPSNGAELLYKRIIRPFFLKHESQMDSVVKDLKDKSKETADAITKEAKKATVNL

HS PKDK

PL LGEEKKST

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for

example, Accession No. R09702) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

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<HP03270> (SEQ ID NOS: 96, 106, and 116)

Determination of the whole base sequence of the cDNA insert of clone HP03270 obtained from cDNA library of human lymphoma cell line U937 revealed the structure consisting of a 132-bp 5'-untranslated region, a 423-bp ORF, and a 656-bp 3'-untranslated region. The ORF encodes a protein consisting of 140 amino acid residues and there existed four putative domains. Figure 36 depicts transmembrane hydrophobicity/hydrophilicity profile, obtained by the Kytemethod, of the present protein. translation resulted in formation of a translation product of 17 kDa that was somewhat larger than the molecular weight of 15,864 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the Schizosaccharomyces pombe hypothetical protein (EMBL Accession No. AL031854). Table 26 shows the comparison between amino acid sequences of the human protein of the present invention (HS) and the Schizosaccharomyces pombe hypothetical protein (SP). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 43.4% in the entire region.

#### Table 26

	НS	MSRFLNVLRSWLVMVSIIAMGNTLQSFRDHTFLYEKLYTGKPNLVNGLQARTFGI
		* *.**. *. **.*** * * * ****
5	SP	${\tt MSQILAMLPDSLVAKWNVVVSVAALFNTVQSFLTPK-LTKRVY-SNTNEVNGLQGRTFGI}$
	HS	${\tt WTLLSSVIRCLCAIDIHNKTLYHITLWTFLLALGHFLSELFVYGTAAPTIGVLAPLMVAS}$
		***** * ** .* ** . * . **** * *.*.*
	SP	WTLLSAIVRFYCAYHITNPDVYFLCQCTYYLACFHFLSEWLLFRTTNLGPGLLSPIVVST
	HS	FSILGMLVGLRYLEVEPVSRQKKRN
10		**
	SP	VSTWFMAKEKASTI.GTAA

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. T30721) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

## <HP03298> (SEQ ID NOS: 97, 107, and 117)

Determination of the whole base sequence of the cDNA insert of clone HP03298 obtained from cDNA library of human lymphoma cell line U937 revealed the structure consisting of a 182-bp 5'-untranslated region, a 462-bp ORF, and a 455-bp 3'-untranslated region. The ORF encodes a protein consisting of 153 amino acid residues and there existed at least one putative transmembrane domain. Figure depicts 37 hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. translation resulted in formation of a translation product of 17.5 kDa that was almost identical with the molecular

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weight of 17,360 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the the Schizosaccharomyces protein was to similar (EMBL Accession SPBC119.09c hypothetical protein AL022117). Table 27 shows the comparison between amino acid sequences of the human protein of the present invention (HS) and the Schizosaccharomyces pombe hypothetical SPBC119.09c (SP). Therein, the marks of -, \*, represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 41.9% in the entire region other than the N-terminal region.

#### Table 27

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA043039) among ESTs. However, since

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they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

5 <HP10631> (SEQ ID NOS: 98, 108, and 118)

Determination of the whole base sequence of the cDNA insert of clone HP10631 obtained from cDNA library of the human retinoblastoma cell line WERI-RB revealed the structure consisting of a 226-bp 5'-untranslated region, a 522-bp ORF, and a 2741-bp 3'-untranslated region. The ORF encodes a protein consisting of 173 amino acid residues and there existed one putative transmembrane domain. Figure 38 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. W26443) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10658> (SEQ ID NOS: 99, 109, and 119)

Determination of the whole base sequence of the cDNA insert of clone HP10658 obtained from cDNA library of the human fibrosarcoma cell line HT-1080 revealed the structure consisting of a 24-bp 5'-untranslated region, a 228-bp ORF, and a 679-bp 3'-untranslated region. The ORF encodes a protein consisting of 75 amino acid residues and there existed two putative transmembrane domains. Figure 39 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In

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vitro translation resulted in formation of a translation product of 14 kDa or less that was almost identical with the molecular weight of 8,625 predicted from the ORF.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. T85006) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

## <HP10663> (SEQ ID NOS: 100, 110, and 120)

Determination of the whole base sequence of the cDNA insert of clone HP10663 obtained from cDNA library of the human lymphoma cell line U937 revealed the structure consisting of a 67-bp 5'-untranslated region, a 480-bp ORF, and a 576-bp 3'-untranslated region. The ORF encodes a protein consisting of 159 amino acid residues and there existed two putative transmembrane domains. Figure 40 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA336522) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

## 30 <HP03165> (SEQ ID NOS: 121, 131, and 141)

Determination of the whole base sequence of the cDNA insert of clone HP03165 obtained from cDNA library of human

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epidermoid carcinoma cell line KB revealed the structure consisting of a 128-bp 5'-untranslated region, a 1911-bp ORF, and a 1195-bp 3'-untranslated region. The ORF encodes a protein consisting of 636 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 41 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 61 kDa that was smaller than the molecular weight of 72,033 predicted from the Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from serine at position 33.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human  $\beta$ -galactosidase (GenBank Protein ID No. AAA51822). Table 28 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the human  $\beta$ -galactosidase (GL). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 37.8% in the entire region.

# Table 28

	HP	MTTWSLRRPARTLGLLLLVVLGFLVLRRLDWSTLVPLRLRHRQLGLQAKGWNFMLEDST
		.** .* .**
5	GL	MPGFLVRILPLLLVLLLLGPTRGLRNATQRMFEIDYSRDSFLKDGQP
	HP	${\tt FWIFGGSIHYFRVPREYWRDRLLKMKACGLNTLTTYVPWNLHEPERGKFDFSGNLDLEAF}$
		***** *** **.***** ***. ****** ***
	GL	${\tt FRYISGSIHYSRVPRFYWKDRLLKMKMAGLNAIQTYVPWNFHEPWPGQYQFSEDHDV{\tt EYF}}$
	HP	${\tt VLMAAEIGLWVILRPGPYICSEMDLGGLPSWLLQDPGMRLRTTYKGFTEAVDLYFDHLMS}$
10		* *.** ******** **** **
	GL	${\tt LRLAHELGLLVILRPGPYICAEWEMGGLPAWLLEKESILLRSSDPDYLAAVDKWLGVLLP}$
	HP	RVVPLQYKRGGPIIAVQVENEYGSY-NKDPAYMPYVKKALEDRGIVELLLTSDNKDG
		** ****.*.******* . * .***
	GL	${\tt KMKPLLYQNGGPVITVQVENEYGSYFACDFDYLAFLQKRFRHHLGDDVVLFTTD{\tt GAHKTF}}$
15	HP	${\tt LSKGIVQGVLATINLQSTHELQLLTTFLFNVQGTQPKMVMEYWTGWFDSWGGPHNILD}$
		*. * .***
	GL	${\tt LKCGALQGLYTTVDFGTGSNITDAFLSQRKCEPKGPLINSEFYTGWLDHWGQPHSTIK}$
	HP	SSEVLKTVSAIVDAGSSINLYMFHGGTNFGFMNGAMHFHDYKSDVTSYDYDAVLTEAGDY
		****** *
20	GL	TEAVASSLYDILARGASVNLYMFIGGTNFAYWNGANSPYAAQPTSYDYDAPLSEAGDL
	HP	TAKYMKLRDFFGSISGIPLPPPPDLLPKMPYEPLTPVLYLSLWDALKYLGEPIKSEKPIN
		*.**. ** * * * ** *
	GL	TEKYFALRNIIQKFEKVPEGPIPPSTPKFAYGKVTLEKLKTVGAALDILC-PSGPIKS
	HP	MENLPVNGGNGQSFGYILYETSITSSGILSGHVHDRGQVFVNTVSIGFLDYKT
<b>25</b>		. * * .*. * * * * * * * * * *
	GL	LYPLTFIQVK-QHYGFVLYRTTLPQDCSNPAPLSSPLNGVHDRAYVAVDGIPQGVLE-RN
	HP	TKIAVPLI-QGYTVLRILVENRGRVNYGENIDDQRKGLIGNLYLNDSPLKNFRIYSL
		*** *** *** **** ***** *** *** *** *** *** *** ***
	GL	NVITLNITGKAGATLDLLVENMGRVNYGAYIND-FKGLVSNLTLSSNILTDWTIFPLDTE
30	HP	DMKKSFFQRFGLDKWSSLPETPTLPAFFLGSLSISSTPCDTFLKLEGWE
		* .** ***** * *** * ***
	GL	DAVRSHLGGWGHRDSGHHDEAWAHNSSNYTLPAFYMGNFSIPSGIPDLPQDTFIQFPGWT
	HP	KGVVFINGQNLGRYW-NIGPQKTLYLPGP-WLSSGINQVIVFEETMAGPALQFTETPHLG
		** *.*** ***** . *** ****. **.*
35	GL	KGQVWINGFNLGRYWPARGPQLTLFVPQHILMTSAPNTITVLELEWAPCSSDDPELCAVT

HP RNQYIK

### GL FVDRPVIGSSVTYDHPSKPVEKRLMPPPPPQKNKDSWLDHV

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA054017) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03266> (SEQ ID NOS: 122, 132, and 142)

Determination of the whole base sequence of the cDNA insert of clone HP03266 obtained from cDNA library of human fibrosarcoma cell line HT-1080 revealed the structure consisting of a 69-bp 5'-untranslated region, a 957-bp ORF, and a 1464-bp 3'-untranslated region. The ORF encodes a protein consisting of 318 amino acid residues and there existed one putative transmembrane domain at the N-terminus. Figure 42 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 34 kDa that was almost identical with the molecular weight of 35,363 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the Arabidopsis thaliana putative ribotol dehydrogenase (GenBank Protein ID No. AAC23625). Table 29 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the

Arabidopsis thaliana putative ribotol dehydrogenase (AT). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 39.0% in the region of 483 residues other than the N-terminal region.

#### Table 29

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HP MVELMFPLLLLLLPFLLYMAAPQIRKMLSSGVCTSTVQLPGKVVVVTGANTGIGKETAKE \* ... . ....\*\*...\*\*\* \*.\*. MGIYGVMTGKKGKSGFGSASTAEDVTQAIDASHLTAIITGGTSGIGLEAARV AT HP LAQRGARVYLACRDVEKGELVAKEIQTTTGNQQVLVRKLDLSDTKSIRAFAKGFLAEEKH . \* . \* . . \* . . \* . . \* . . . \* \* . . . 15 AT LAMRGAHVIIAARNPKAANESKEMILQMNPNARVDYLQIDVSSIKSVRSFVDQFLALNVP HP LHVLINNAGVMMCPYSKTADGFEMHIGVNHLGHFLLTHLLLEKLK----ESAPSRIVNV \*..\*\*\*\*\*\*\*.\*\*.. \*.\*\*.\* ....\*\*.\*\*\*\*\*\* AT LNILINNAGVMFCPFKLTEDGIESOFATNHIGHFLLTNLLLDKMKSTARESGVQGRIVNL HP SSLAH---HLGRIHFHNLQGEKFYNAGLAYCHSKLANILFTQELARRLKGSG--VTTYSV 20 AT SSIAHTYTYSEGIKFQGINDPAGYSERRAYGQSKLSNLLHSNALSRRLQEEGVNITINSV HP HPGTVOSELVRHSSFMRWMWWLFSF-FIKTPQQGAQTSLHCALTEGLEILSGNHFSDCHV AT HPGLVTTNLFRYSGFSMKVFRAMTFLFWKNIPQGAATTCYVALHPDLEGVTGKYFGDCNI 25 HP AWVSAQARNETIARRLWDVSCDLLGLPID \* \* \* . . . \* . \* \* \* . .

AT VAPSKFATNNSLADKLWDFSVFLIDSISK

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. D17020) among ESTs. However, since

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they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

5 <HP03287> (SEQ ID NOS: 123, 133, and 143)

Determination of the whole base sequence of the cDNA insert of clone HP03287 obtained from cDNA library of human thymus revealed the structure consisting of a 83-bp 5'untranslated region, a 249-bp ORF, and a 1133-bp untranslated region. The ORF encodes a protein consisting of 82 amino acid residues and there existed one putative transmembrane domain at the N-terminus and one at the Cterminus, respectively. Figure 43 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kytemethod, of the present protein. translation resulted in formation of a translation product of high molecular weight.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the Schizosaccharomyces hypothetical protein 9.0kDa (SWISS-PROT Accession No. 013825). Table 30 shows the comparison between amino acid sequences of the human protein of the present invention (HP) Schizosaccharomyces pombe hypothetical 9.0kDa (SP). Therein, the marks of -, \*, and . represent a an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 45.7% in the entire region.

#### Table 30

HP MAFTLYSLLQAALLCVNAIAVLHEERFLKNIGWGTDQGIGGFGE-EPGIKSQLMNLIRSV
\*...\* .\*\* .\*\* \* .\*\*\* .\*\*\*. ... \*\*\*... .\*\*\*...

SP MFGFGNILYVTLLLLNAVAILSEDRFLGRIGWSQSAAL-GFGDRQDTIKSRILHLIRAI

HP RTVMRVPLIIVNSIAIVLLLLFG

\*\*\*\* \*\*\* \*\*\* \* . \*

SP RTVMTFPLIAINTIVIVYNLVLG

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA853098) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10665> (SEQ ID NOS: 124, 134, and 144)

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Determination of the whole base sequence of the cDNA insert of clone HP10665 obtained from cDNA library of human fibrosarcoma cell line HT-1080 revealed the structure consisting of a 31-bp 5'-untranslated region, a 744-bp ORF, and a 142-bp 3'-untranslated region. The ORF encodes a protein consisting of 247 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 44 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 28 kDa that was somewhat larger than the molecular weight of 25,320 predicted from the ORF. In this case, the addition of a microsome led to the formation

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of a product of 27 kDa. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from aspertic acid at position 26.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA055367) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10669> (SEQ ID NOS: 125, 135, and 145)

Determination of the whole base sequence of the cDNA insert of clone HP10669 obtained from cDNA library of human retinoblastoma cell line WERI-RB revealed the structure consisting of a 73-bp 5'-untranslated region, a 621-bp ORF, and a 612-bp 3'-untranslated region. The ORF encodes a protein consisting of 206 amino acid residues and there existed one putative transmembrane domain. Figure 45 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AF086533) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

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<HP10670> (SEQ ID NOS: 126, 136, and 146)

Determination of the whole base sequence of the cDNA

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insert of clone HP10670 obtained from cDNA library of human retinoblastoma cell line WERI-RB revealed the structure consisting of a 117-bp 5'-untranslated region, a 1299-bp ORF, and a 606-bp 3'-untranslated region. The ORF encodes a protein consisting of 432 amino acid residues and there existed seven putative transmembrane domains. Figure 46 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein.

The search of the protein data base using the amino acid sequence of the present protein revealed that the Caenorhabditis elegans similar to the protein was hypothetical protein CELM03F8.2 (GenBank Protein ID No. AAB65910). Table 31 shows the comparison between amino acid sequences of the human protein of the present invention (HP) hypothetical elegans Caenorhabditis CELM03F8.2 (CE). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 39.6% in the N-terminal region of 376 residues.

## Table 31

	HP	MDARWWAVVVLAAFPSLGAGGETPEAPPESWTQLWFFRFVVNAAGYASFMVPGYLLVQYF
		** ** ** ** *
5	CE	MDRSIMPIDSPARDKPPDELVWPLRLFLILLGYSTVATPAAILIYYV
	HP	RRKNYLETGRGLCFPLVKACVFGNEPKASDEVPLAPRTEAAETTPMWQALKL
		** ** *
	CE	RRNRHAFETPYLSIRLILRS-FAVGNPEYQLIPTGEKQARKENDSIPQTRAQCINVIILL
	HP	LFCATGLQVSYLTWGVLQERVMTRSY-GATATSPGERFTDSQFLVLMNRVLALIVAGL
10		** .*.** . ******
	CE	LFFFSGIQVTLVAMGVLQERIITRGYRRSDQLEVEDKFGETQFLIFCNRIVALVLSLMIL
	HP	SCVLCKQPRHGAPMYRYSFASLSNVLSSWCQYEALKFVSFPTQVLAKASKVIPVMLMGKL
		***** * ** * * * * * * * * * * * * * * *
	CE	AKDWTKQPPHVPPLYVHSYTSFSNTISSWCQYEALKYVSFPTQTICKASKVVVTMLMGRL
15	HP	VSRRSYEHWEYLTATLISIGVSMFLLSSGPEPRSSPATTLSGLILLAGYIAFDSFTSN
		**** . **.*****
	CE	VRGQRYSWFEYGCGCTIAFGASLFLLSSSSKGAGSTITYTSFSGMILMAGYLLFDAFTLN
	HP	WQDALFAYKMSSVQMMFGVNFFSCLFTVGSLLEQGALLEGTRFMGRHSEFAAHALLLS
		**.***. * .*. ******** **.**.** . * .**
20	CE	WQKALFDTKPKVSKYQMMFGVNFFSAILCAVSLIEQGTLWSSIKFGAEHVDFSRDVFLLS
	HP	ICSACGQLFIFYTIGQFGAAVFTIIMTLRQAFAILLSCLLYGHTVTVVGGLGVAVVFAAL
		* **.**. ****. ****
	CE	LSGAIGQIFIYSTIERFGPIVFAVIMTIRQIFIRNTLIRAEDHRGVEMAPPPPPEPFRLK
	HP	LLRVYARGRLKQRGKKAVPVESPVQKV
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	CE	FLSMIIAVIHI

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. Z46196) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the

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present invention.

<HP10671> (SEQ ID NOS: 127, 137, and 147)

Determination of the whole base sequence of the cDNA insert of clone HP10671 obtained from cDNA library of human thymus revealed the structure consisting of a 74-bp 5'-921-bp ORF, and a untranslated region, a untranslated region. The ORF encodes a protein consisting of amino acid residues and there existed a N-terminus and putative one secretory signal at the transmembrane domain at the intermediate region. Figure 47 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA357141) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10673> (SEQ ID NOS: 128, 138, and 148)

Determination of the whole base sequence of the cDNA insert of clone HP10673 obtained from cDNA library of the human thymus revealed the structure consisting of a 203-bp 5'-untranslated region, a 1668-bp ORF, and a 339-bp 3'untranslated region. The ORF encodes a protein consisting of 555 amino acid residues and there existed one putative the 48 depicts transmembrane domain. Figure hydrophobicity/hydrophilicity profile, obtained by the Kytepresent protein. Doolittle method, of the translation resulted in formation of a translation product

of 65 kDa that was somewhat larger than the molecular weight of 61,781 predicted from the ORF.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. R96413) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

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<HP10675> (SEQ ID NOS: 129, 139, and 149)

Determination of the whole base sequence of the cDNA insert of clone HP10675 obtained from cDNA library of the human thymus revealed the structure consisting of a 92-bp 5'-untranslated region, a 753-bp ORF, and a 648-bp 3'-untranslated region. The ORF encodes a protein consisting of 250 amino acid residues and there existed at least one putative transmembrane domain. Figure 49 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA356139) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10683> (SEQ ID NOS: 130, 140, and 150)

30 Determination of the whole base sequence of the cDNA insert of clone HP10683 obtained from cDNA library of the human lymphoma cell line U937 revealed the structure

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consisting of a 25-bp 5'-untranslated region, a 525-bp ORF, and a 714-bp 3'-untranslated region. The ORF encodes a protein consisting of 174 amino acid residues and there existed one putative transmembrane domain. Figure 50 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 22 kDa that was somewhat larger than the molecular weight of 19,572 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 24 kDa to which sugar chains are presumably attached. In addition, there exist in the amino acid sequence of this protein one site at which N-glycosylation may occur (Asn-Ile-Thr at position 27).

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA482321) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

## INDUSTRIAL APPLICABILITY

The present invention provides human proteins having hydrophobic domains, DNAs encoding these proteins, and expression vectors for these DNAs as well as eukaryotic cells expressing these DNAs. Since all of the proteins of the present invention are secreted or exist in the cell membrane, they are considered to be proteins controlling the proliferation and/or the differentiation of the cells. Accordingly, the proteins of the present invention can be employed as pharmaceuticals such as carcinostatic agents

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which to control the proliferation and/or differentiation of the cells, or as antigens for preparing antibodies against these proteins. The DNAs of the present invention can be utilized as probes for the diagnosis and gene sources for the gene therapy. Furthermore, the DNAs can be utilized for large-scale expression of these proteins. Cells into which these genes are introduced to express these proteins, can be utilized for detection of the corresponding receptors or ligands, screening of novel small molecule pharmaceuticals and the like.

The present invention also provides genes corresponding to the polynucleotide sequences disclosed herein. "Corresponding genes" are the regions of the genome that are transcribed to produce the mRNAs which from CDNA polynucleotide sequences are derived and mav include contiguous regions of the genome necessary for the regulated expression of such genes. Corresponding genes may therefore include but are not limited to coding sequences, 5' and 3' untranslated regions, alternatively spliced exons, introns, promoters, enhancers, and silencer or suppressor elements. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials. An "isolated gene" is a gene that has been separated from the adjacent coding sequences, if any, present in the genome of the organism from which the gene was isolated.

Organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein are provided. The

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desired change in gene expression can be achieved through the use of antisense polynucleotides or ribozymes that bind and/or cleave the mRNA transcribed from the gene (Albert and Sci. 15(7): 250-254; Morris, 1994, Trends Pharmacol. Lavarosky et al., 1997, Biochem. Mol. Med. 62(1): 11-22; and Hampel, 1998, Prog. Nucleic Acid Res. Mol. Biol. 58: 1-39; incorporated by reference which are Transgenic animals that have multiple copies of the gene(s) the polynucleotide sequences disclosed corresponding to herein, preferably produced by transformation of cells with genetic constructs that are stably maintained within the progeny, provided. their are transformed cells and animals that have modified genetic control Transgenic regions that increase or reduce gene expression levels, or that change temporal or spatial patterns of gene expression, are also provided (see European Patent No. 0 649 464 B1, incorporated by reference herein). In addition, organisms are provided in which the gene(s) corresponding to the disclosed sequences herein have polynucleotide partially or completely inactivated, through insertion of extraneous sequences into the corresponding gene(s) through deletion of all or part of the corresponding gene(s). Partial or complete gene inactivation can be accomplished through insertion, preferably followed by imprecise excision, of transposable elements (Plasterk, 1992, Bioessays 14(9): 629-633; Zwaal et al., 1993, Proc. Natl. Acad. Sci. USA 90(16): 7431-7435; Clark et al., 1994, Proc. Natl. Acad. Sci. 91(2): 719-722; all of which are incorporated by reference herein), or through homologous recombination, preferably detected by positive/negative genetic selection strategies (Mansour et al., 1988, Nature 336: 348-352; U.S. Patent Nos. 5,464,764; 5,487,992; 5,627,059; 5,631,153;

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396; 5,616,491; and 5,679,523; all of which are incorporated by reference herein). These organisms with altered gene expression are preferably eukaryotes and more preferably are mammals. Such organisms are useful for the development of non-human models for the study of disorders involving the corresponding gene(s), and for the development of assay systems for the identification of molecules that interact with the protein product(s) of the corresponding gene(s). Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be in accordance with identified techniques for determination of such domains from sequence information.

Proteins and protein fragments of the present invention include proteins with amino acid sequence lengths that are at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of a disclosed protein and have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein, where sequence identity is determined by comparing the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Also included in the present invention are proteins and protein fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that shares at least 75%

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sequence identity (more preferably, at least 85% identity; most preferably at least 95% identity) with any such segment of any of the disclosed proteins.

Species homologs of the disclosed polynucleotides and proteins are also provided by the present invention. As used herein, a "species homologue" is a protein or polynucleotide with a different species of origin from that of a given protein or polynucleotide, but with significant sequence similarity to the given protein or polynucleotide, as determined by those of skill in the art. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous, or related to that encoded by the polynucleotides.

The invention also includes polynucleotides with sequences complementary to those of the polynucleotides disclosed herein.

The present invention also includes polynucleotides capable of hybridizing under reduced stringency conditions, more preferably stringent conditions, and most preferably highly stringent conditions, to polynucleotides described herein. Examples of stringency conditions are shown in the Table 32 below: highly stringent conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for example, conditions M-R.

Table 32

Stringency	Polynucleotide	Hybrid	Hybridization Temperature	Wash
Condition	Hybrid	Length	and Buffer <sup>†</sup>	Temperature
		(bp) <sup>‡</sup>		and Buffer†
A	DNA: DNA	≥50	65°C; 1×SSC -or-	65°C; 0.3×SSC
			42°C; 1×SSC,50% formamide	
В	DNA: DNA	<50	T <sub>B</sub> *; 1×SSC	T <sub>B</sub> *; 1×SSC
C	DNA: RNA	≥50	67°C; 1×SSC -or-	67°C; 0.3×SSC
			45°C; 1×SSC,50% formamide	
D	DNA: RNA	<50	T <sub>D</sub> *; 1×SSC	T <sub>D</sub> *; 1×SSC
E	RNA: RNA	≥50	70℃; 1×SSC -or-	70°C; 0.3×SSC
			50°C; 1×SSC,50% formamide	
F	RNA: RNA	<50	T <sub>F</sub> *; 1×SSC	T <sub>F</sub> *; 1×SSC
G	DNA: DNA	≥50	65°C; 4×SSC -or-	65°C; 1×SSC
ļ			42°C; 4×SSC,50% formamide	
H	DNA : DNA	<50	T <sub>H</sub> *; 4×SSC	T <sub>H</sub> *; 4×SSC
I	DNA: RNA	≥50	67°C; 4×SSC -or-	67°C; 1×SSC
			45°C; 4×SSC,50% formamide	
J	DNA: RNA	<50	T <sub>J</sub> *; 4×SSC	T <sub>J</sub> *; 4×SSC
K	RNA: RNA	≥50	70°C; 4×SSC -or-	67°C; 1×SSC
			50°C; 4×SSC,50% formamide	
L	RNA: RNA	<50	T <sub>L</sub> *; 2×SSC	T <sub>L</sub> *; 2×SSC
M	DNA : DNA	≥50	50°C; 4×SSC -or-	50°C; 2×SSC
			40°C; 6×SSC,50% formamide	
N	DNA: DNA	<50	T <sub>N</sub> *; 6×SSC	T <sub>N</sub> *; 6×SSC
O	DNA : RNA	≥50	55°C; 4×SSC -or-	55°C; 2×SSC
			42°C; 6×SSC,50% formamide	
P	DNA: RNA	<50	T <sub>P</sub> *; 6×SSC	T <sub>P</sub> *; 6×SSC
Q	RNA: RNA	≥50	60°C; 4×SSC -or-	60°C; 2×SSC
			45°C; 6×SSC,50% formamide	
R	RNA: RNA	<50	T <sub>R</sub> *; 4×SSC	T <sub>R</sub> *; 4×SSC

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‡: The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.

†: SSPE (1×SSPE is 0.15M NaCl, 10mM NaH<sub>2</sub>PO<sub>4</sub>, and 1.25mM EDTA, pH7.4) can be substituted for SSC (1×SSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.

\* $T_B$  -  $T_R$ : The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature ( $T_m$ ) of the hybrid, where  $T_m$  is determined according to the following equations. For hybrids less than 18 base pairs in length,  $T_m$ (°C)=2(#of A + T bases) + 4(# of G + C bases). For hybrids between 18 and 49 base pairs in length,  $T_m$ (°C)=81.5 + 16.6(log<sub>10</sub>[Na<sup>+</sup>]) + 0.41 (%G+C) - (600/N), where N is the number of bases in the hybrid, and [Na<sup>+</sup>] is the concentration of sodium ions in the hybridization buffer ([Na<sup>+</sup>] for 1×SSC=0.165M).

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Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and Current Protocols in Molecular Biology, 1995, F.M. Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Preferably, each such hybridizing polynucleotide has a length that is at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of the polynucleotide of the present invention to which it hybridizes, and has at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with the polynucleotide of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the hybridizing

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polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps.

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#### CLAIMS

- 1. A protein comprising any one of an amino acid sequence selected from the group consisting of SEQ ID NOS: 1 to 10, 31 to 40, 61 to 70, 91 to 100, and 121 to 130.
- 2. An isolated DNA encoding the protein according to Claim 1.
- 3. An isolated cDNA comprising any one of a base sequence selected from the group consisting of SEQ ID NOS: 11 to 20, 41 to 50, 71 to 80, 101 to 110, and 131 to 140.
- 4. The cDNA according to Claim 3 consisting of any one of a base sequence selected from the group consisting of SEQ ID NOS: 21 to 30, 51 to 60, 81 to 90, 111 to 120, and 141 to 150.
- 5. An expression vector that is capable of expressing the DNA according to any one of Claim 2 to Claim 4 by in vitro translation or in eukaryotic cells.
- 6. A transformed eukaryotic cell that is capable of expressing the DNA according to any one of Claim 2 to Claim 2 and of producing the protein according to Claim 1.



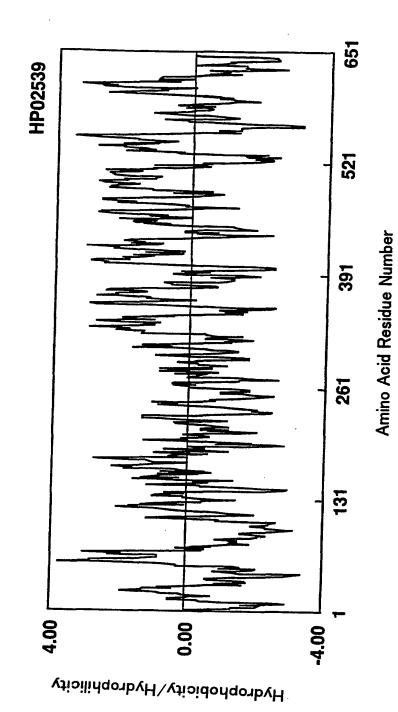


Fig.2

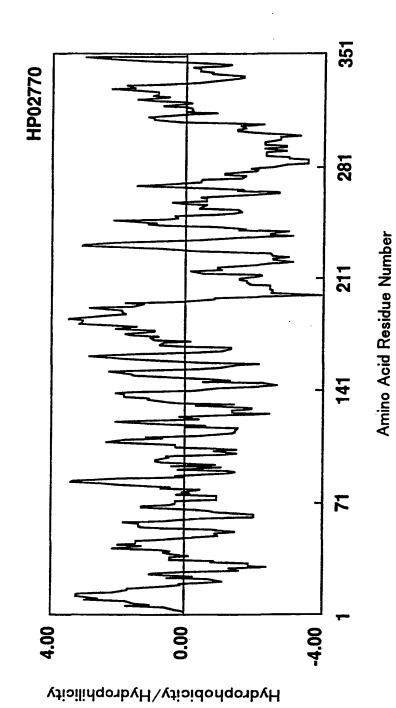
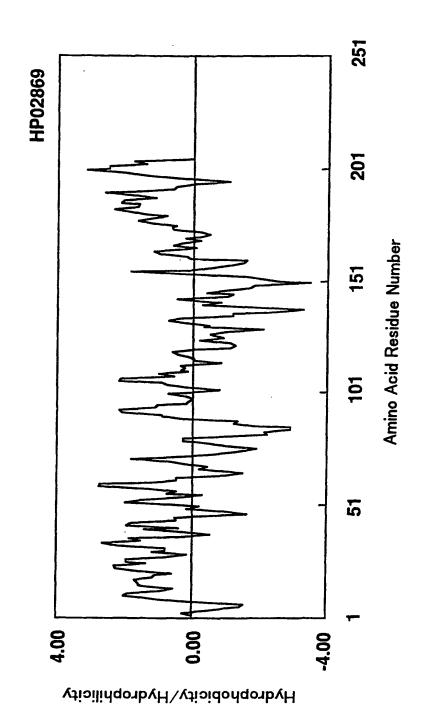
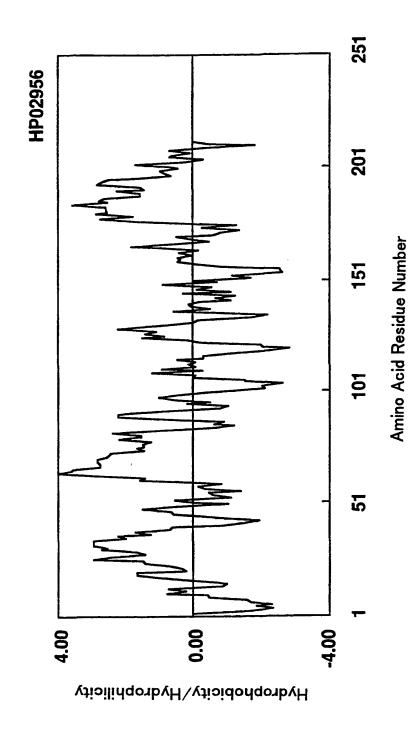


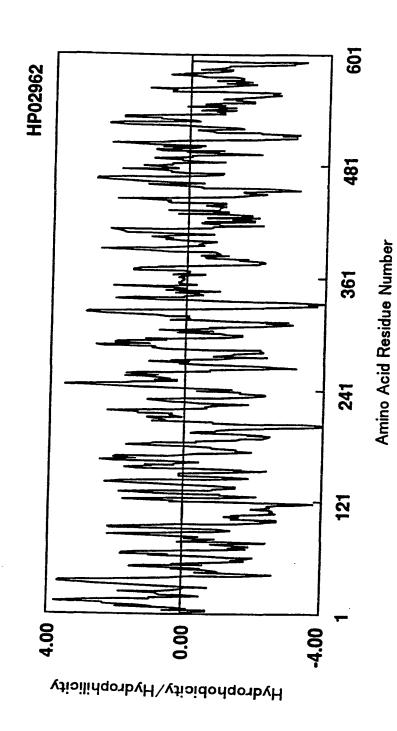
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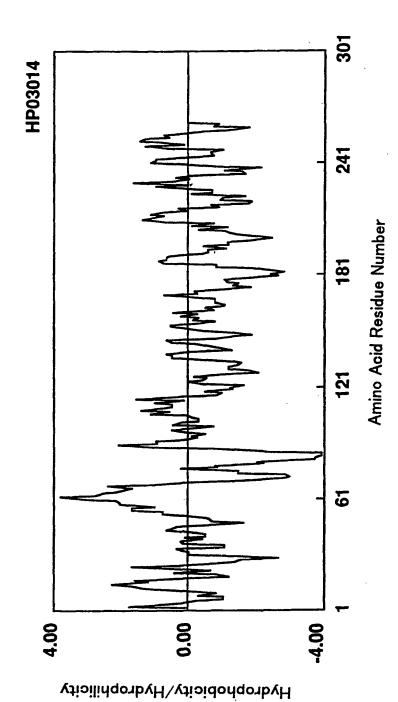




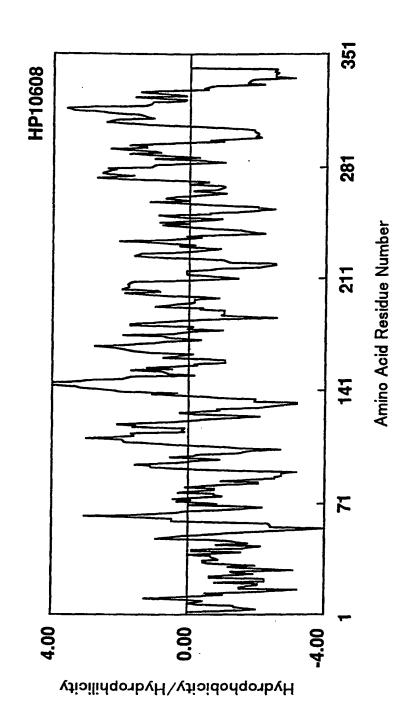




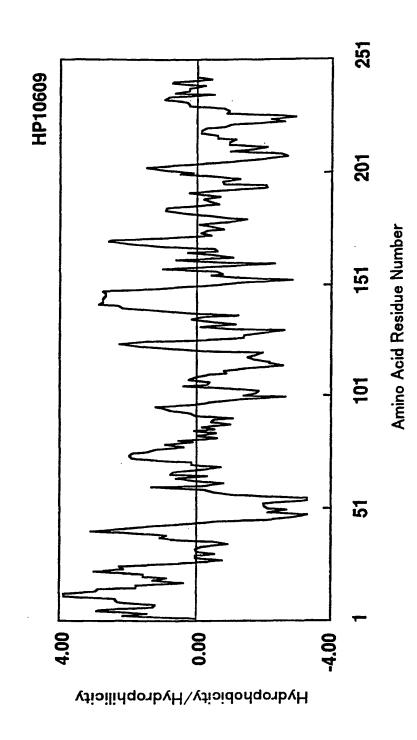




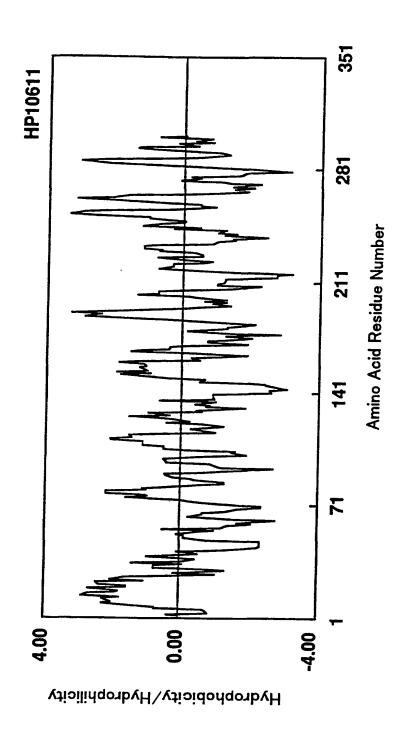




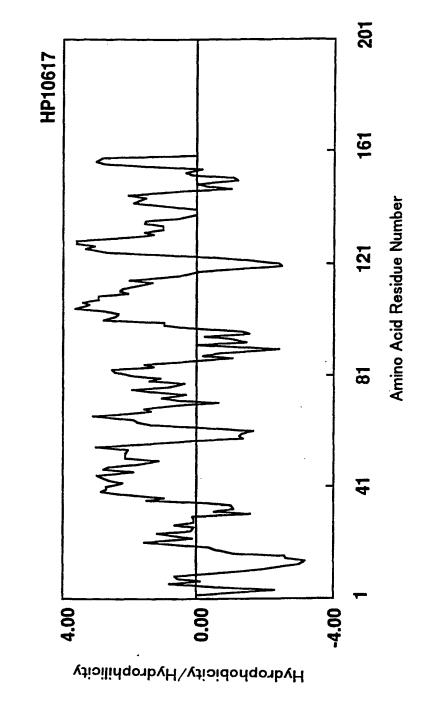


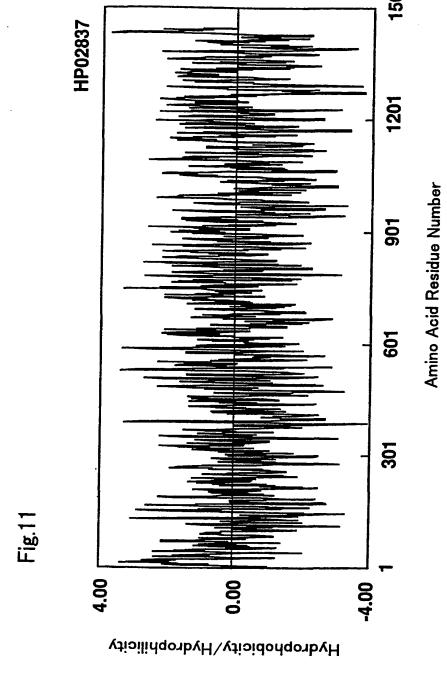


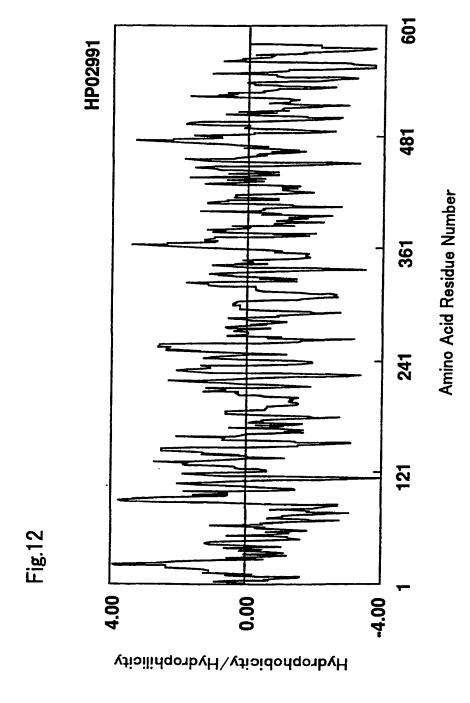




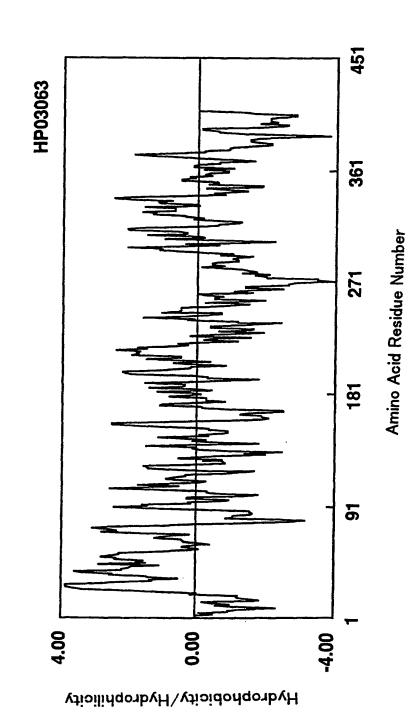
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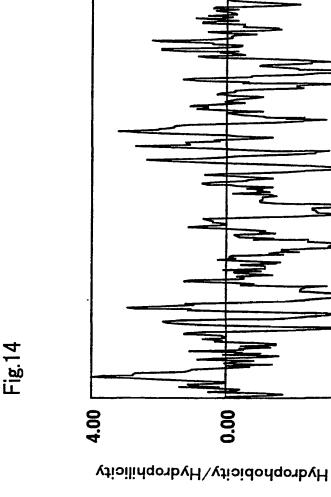








Amino Acid Residue Number



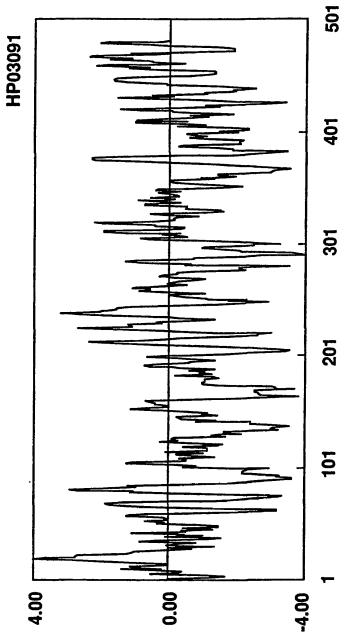
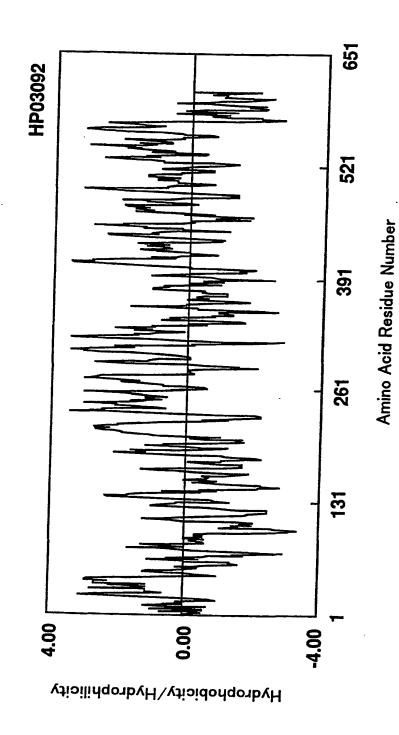
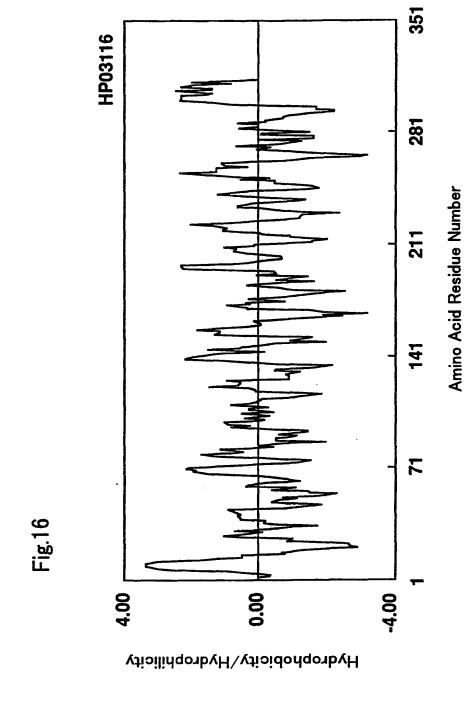
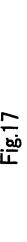
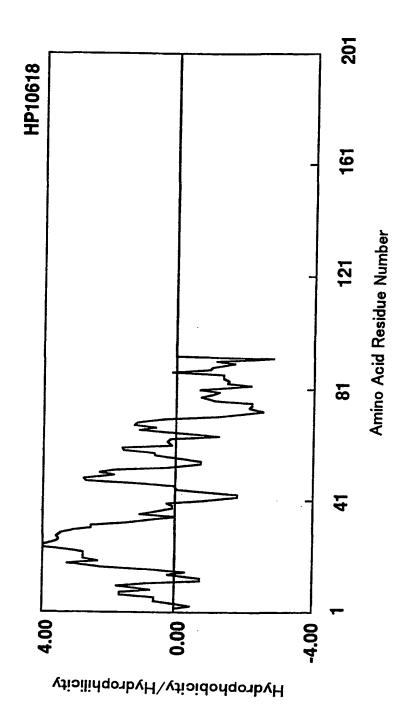


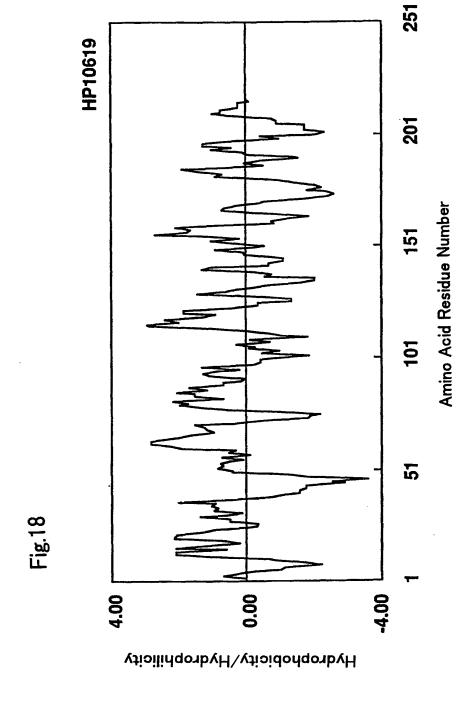
Fig. 15



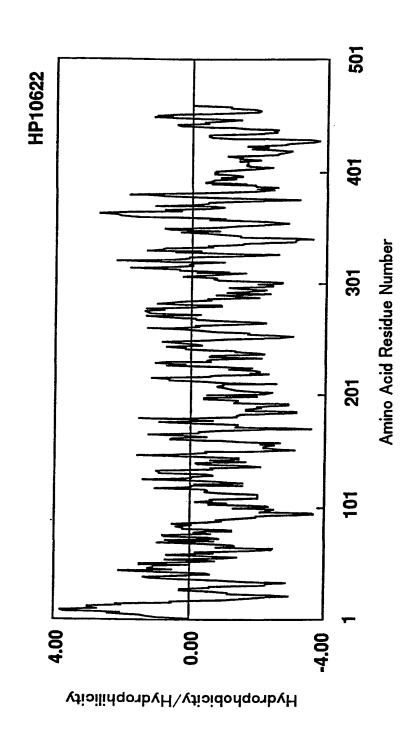


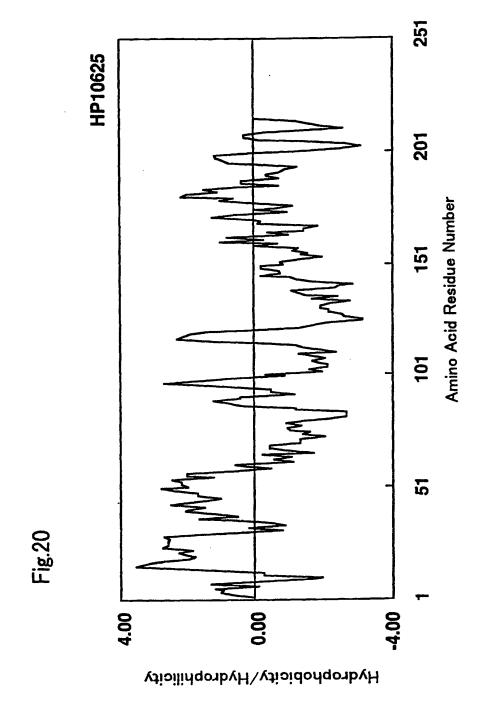


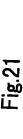


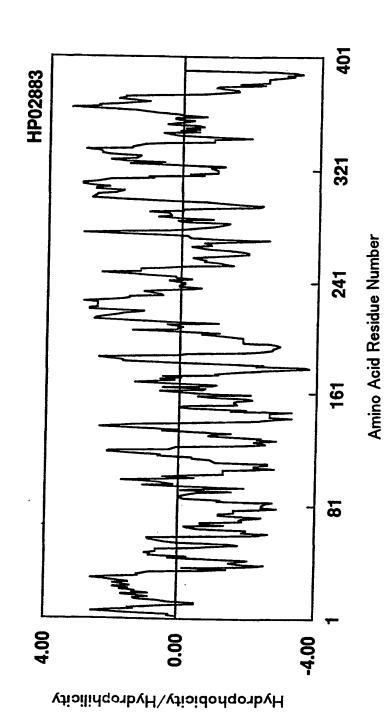














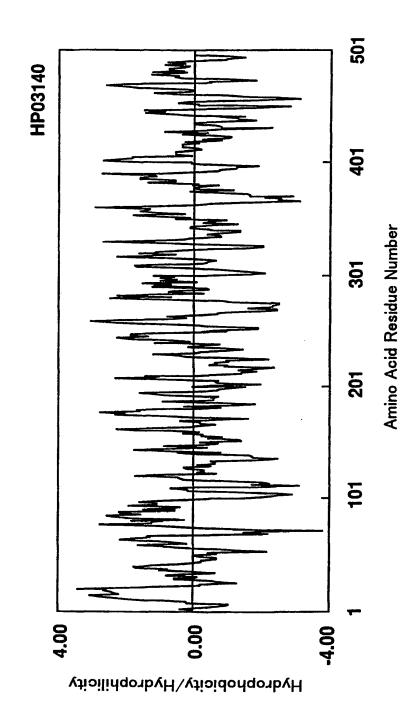




Fig.23

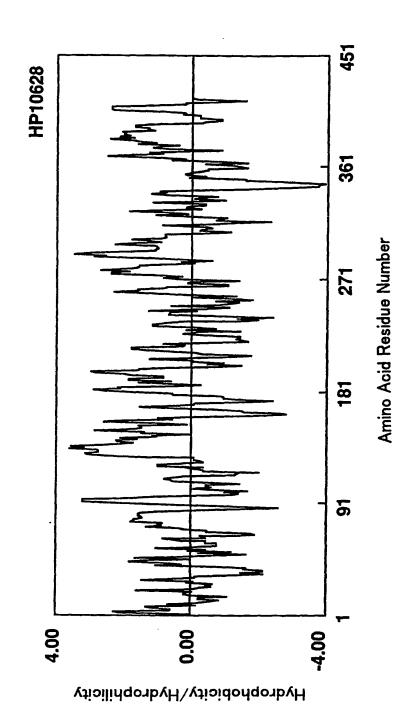
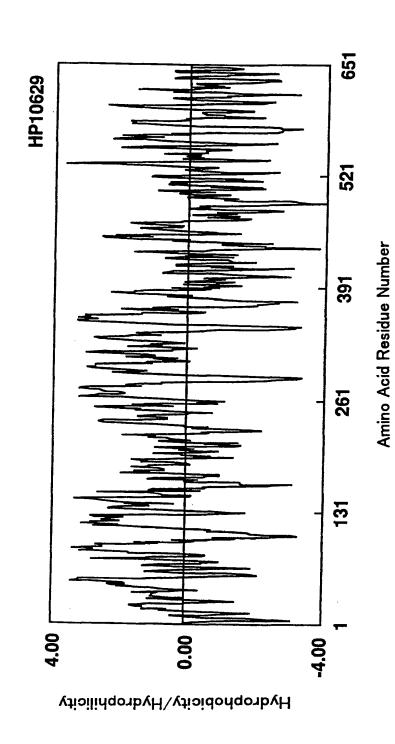
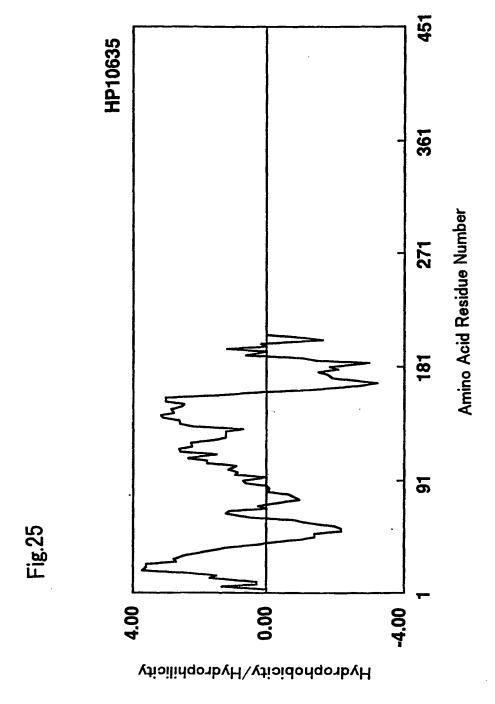


Fig.24





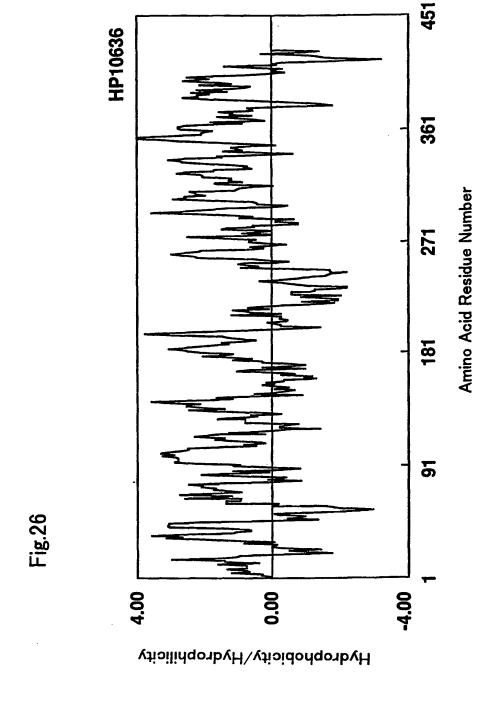
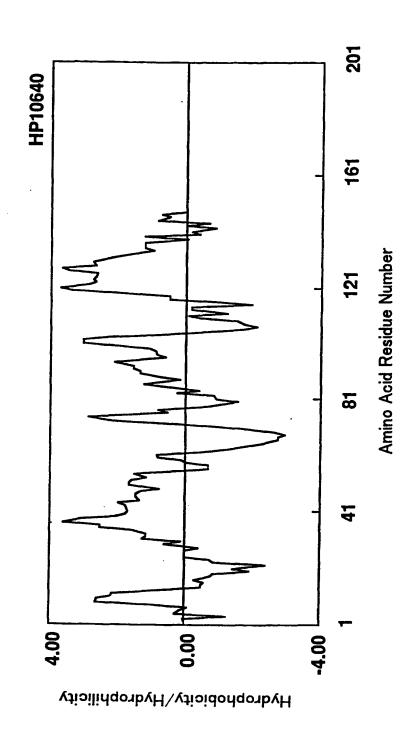
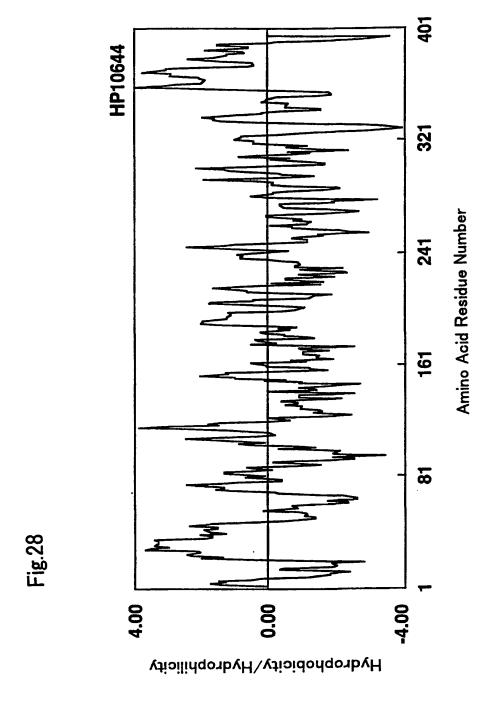
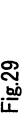
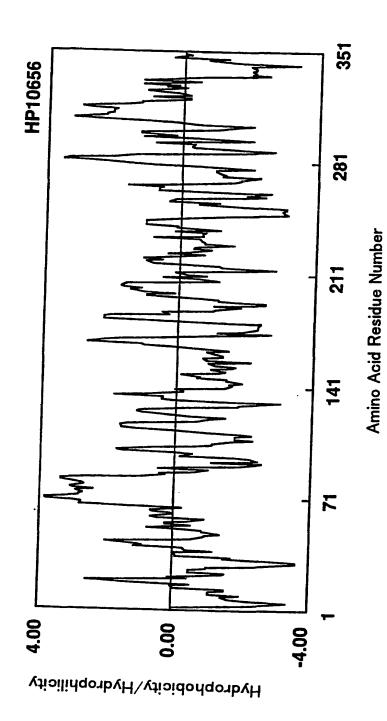


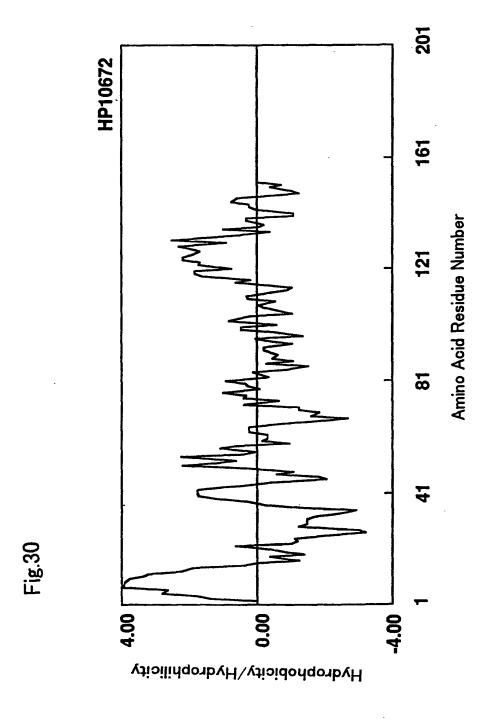
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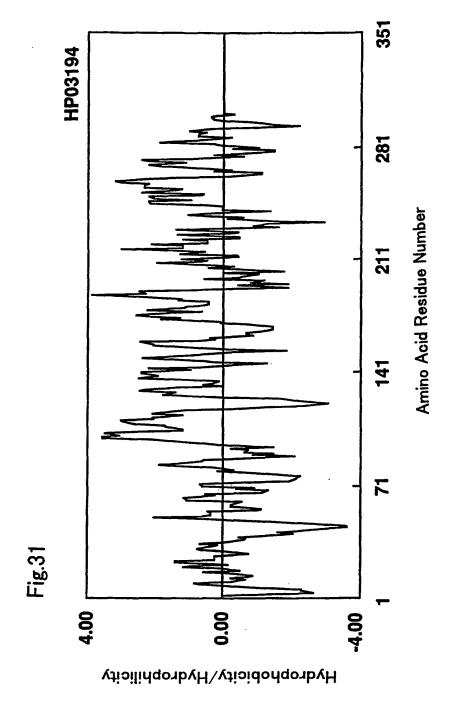


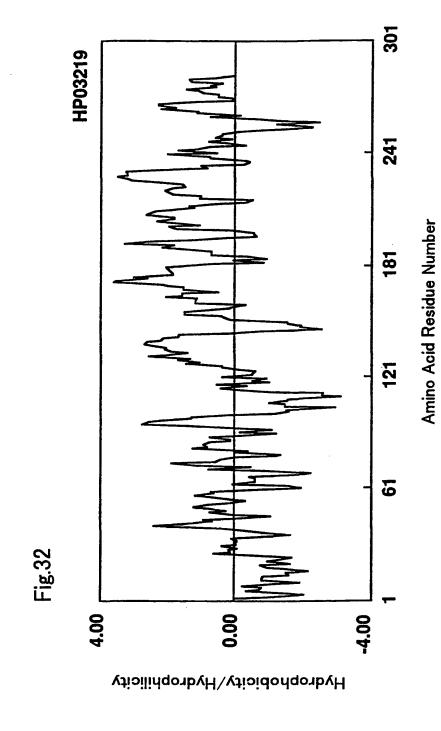


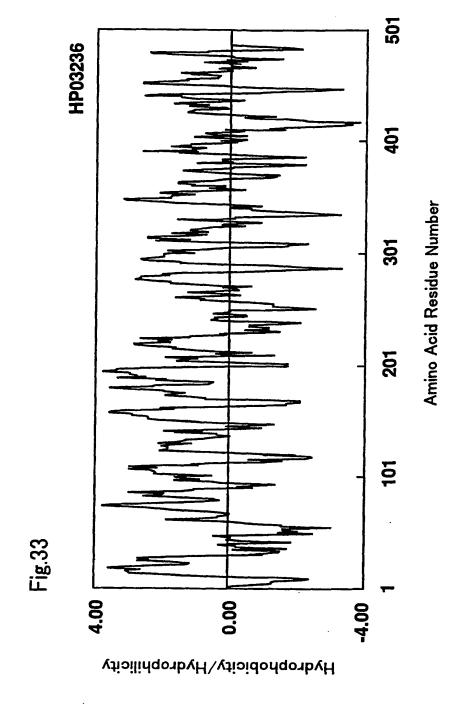


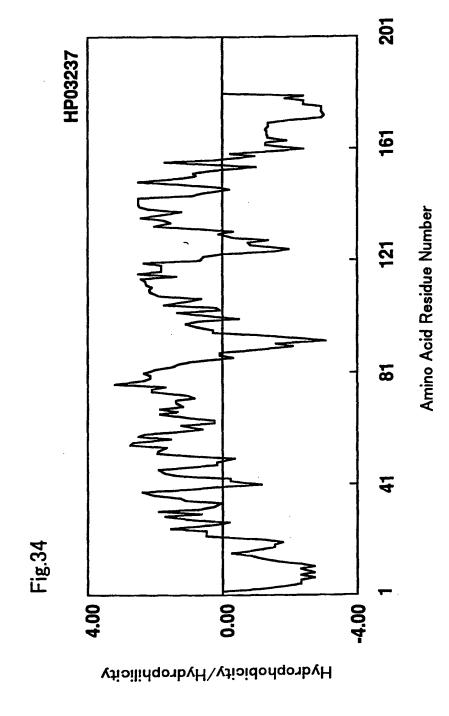


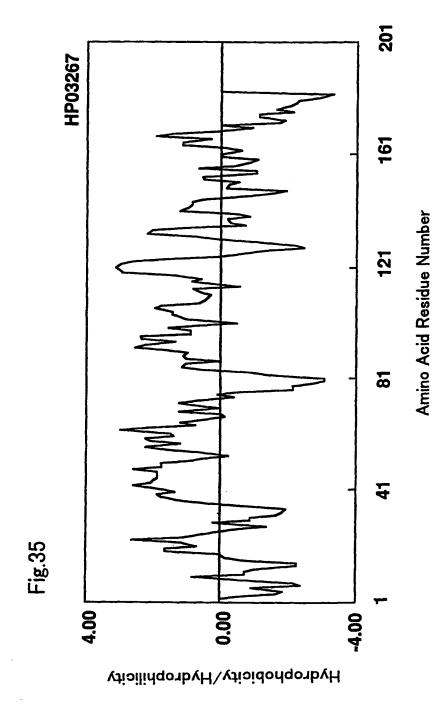


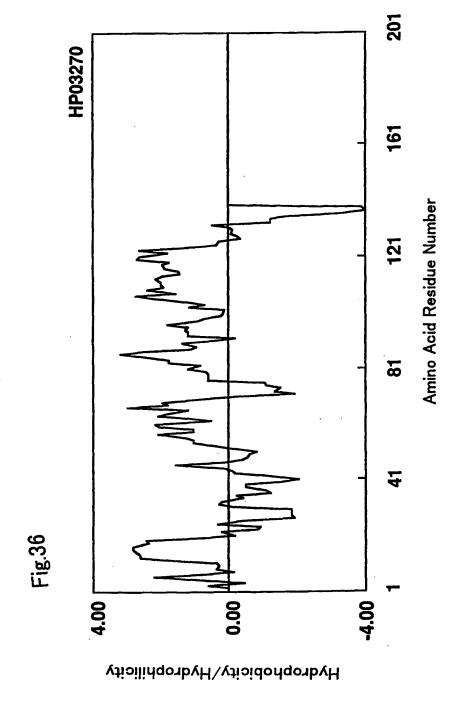


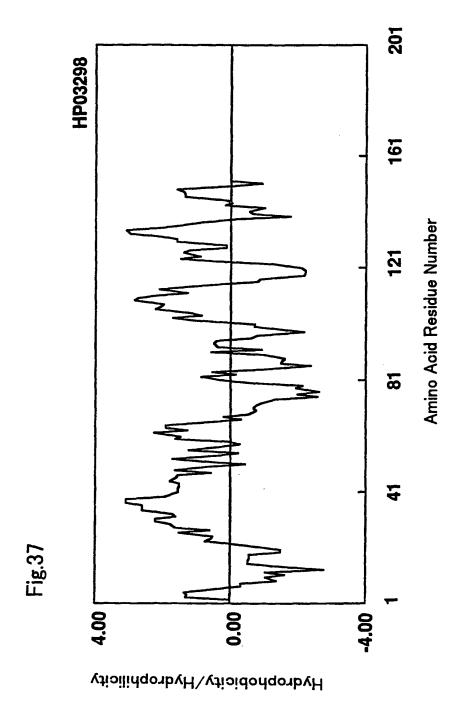


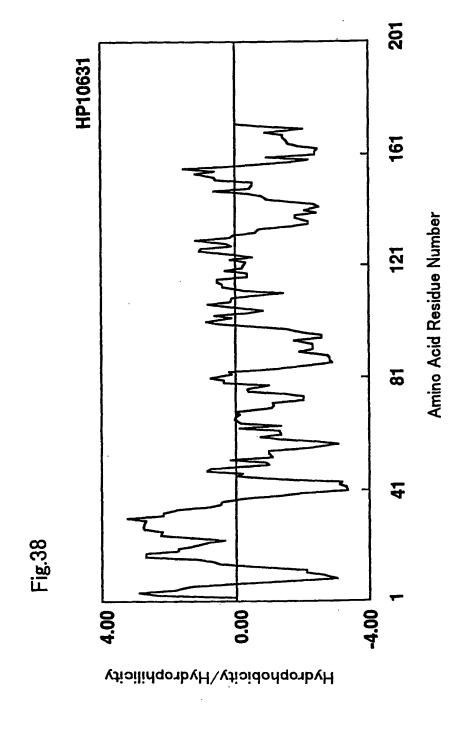


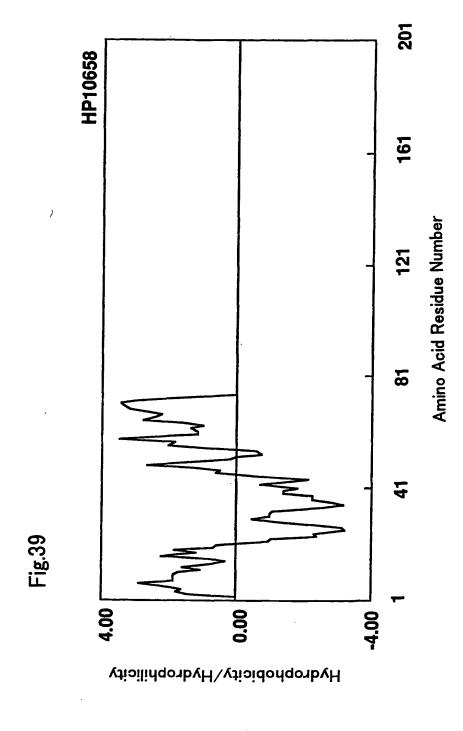












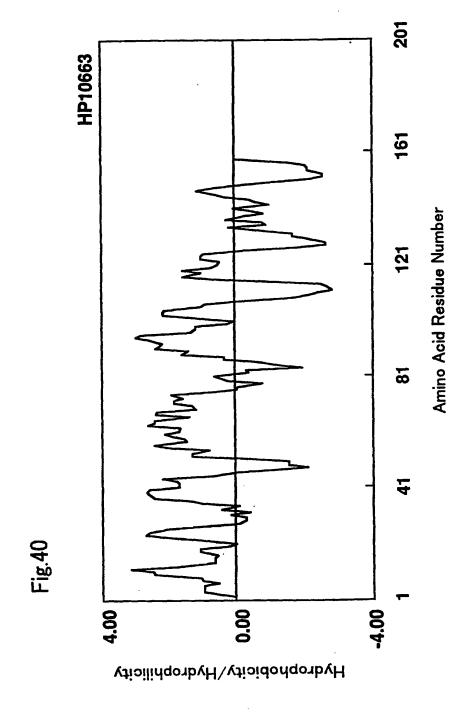
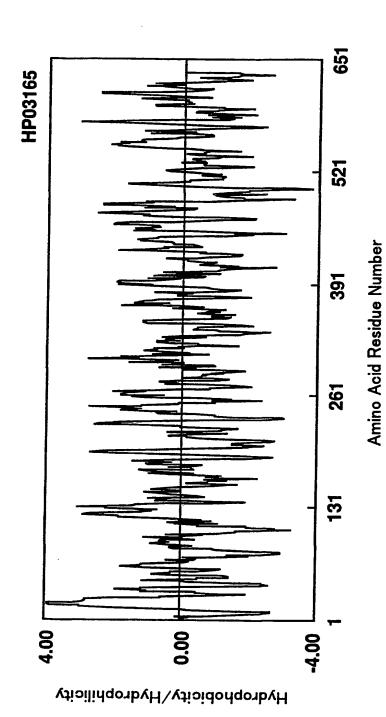
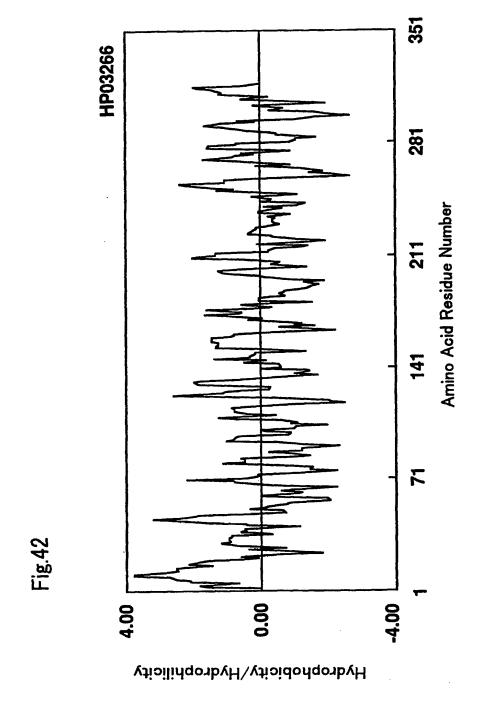
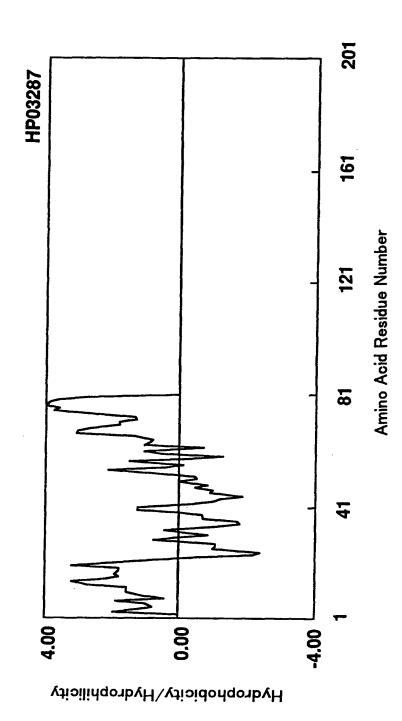


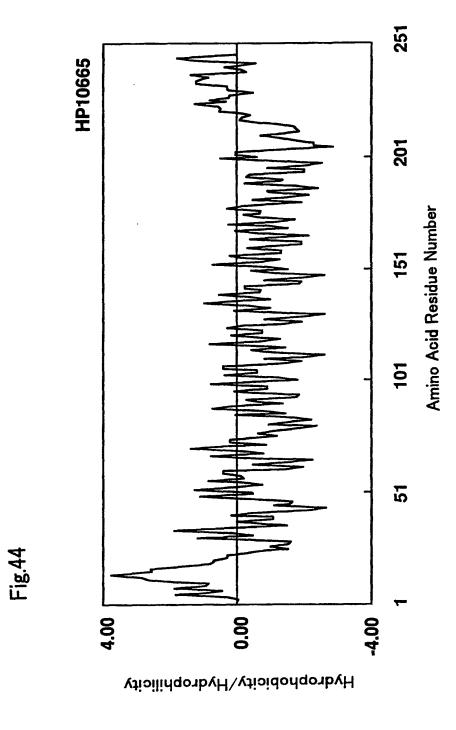
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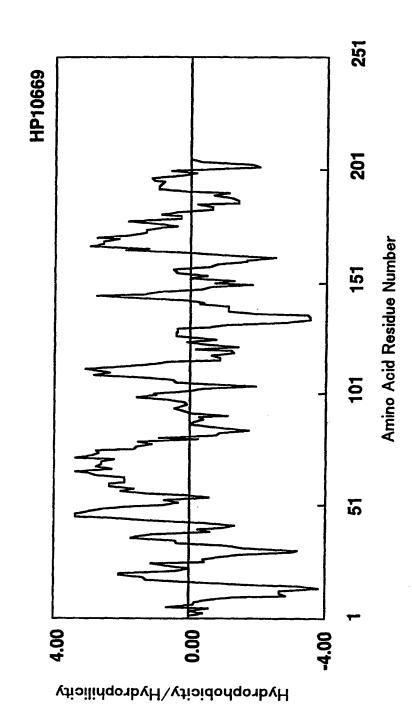


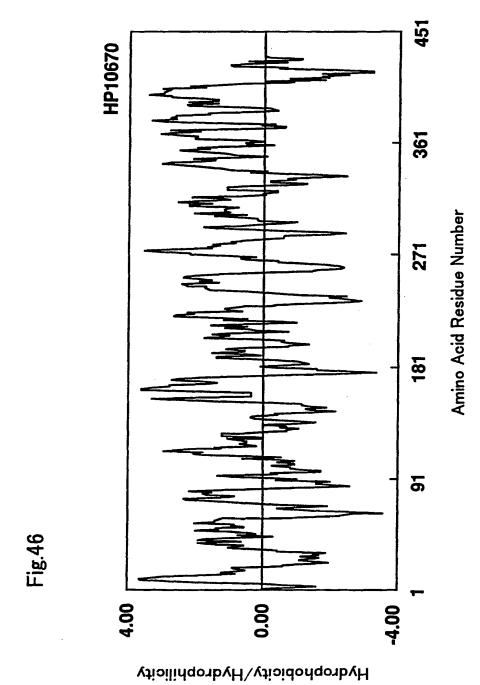


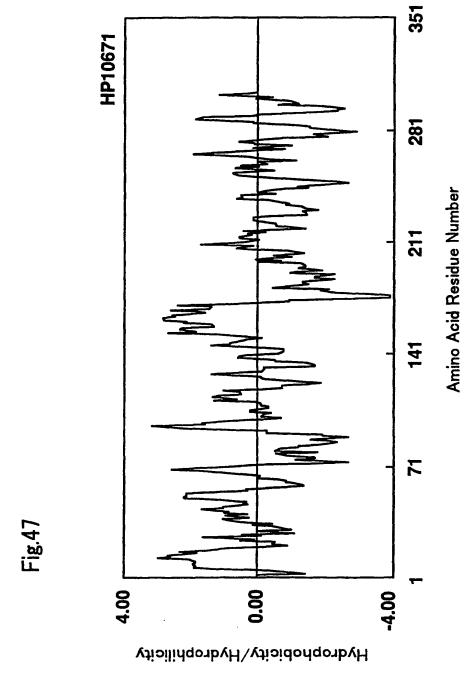




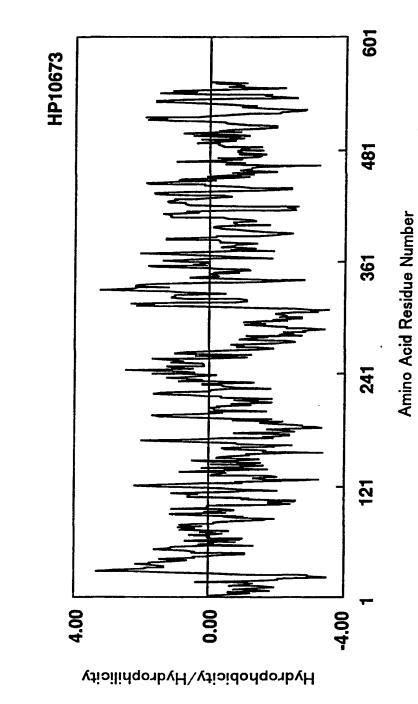




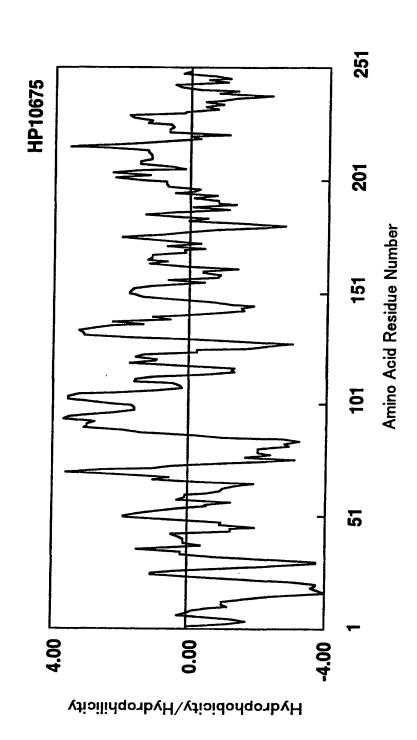




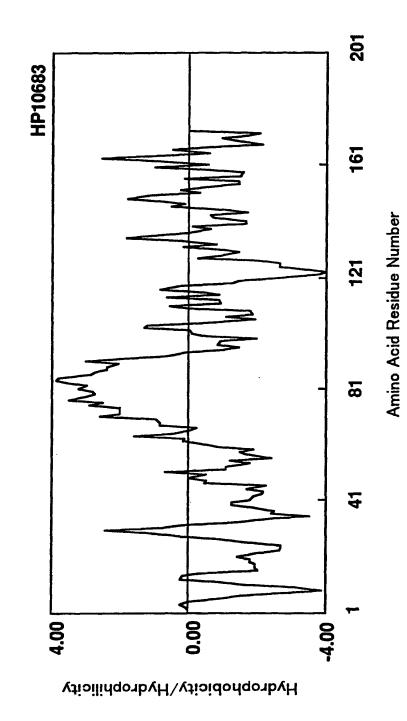














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Cys	Ser	Ala	Glu	Leu	Lys	Phe	Phe	Leu	_	Ser	Met	Tyr	Ala		Val		
_				165		_			170					175			
Cys	Thr	Val		Glu	Gln	Ala	Leu		Pro	Cys	Arg	Ser		Cys	Glu		
•		•	180	<b>~</b> 3	<b>.</b>			185		_	_	_,	190				
Arg	ATa		GIN	Gly	Cys	GIU		Leu	Met	Asn	Lys		GIY	Pne	GIN		
Mana	n	195	mb	T	T	<b>~</b>	200	T	DL -	<b>D</b>	**_ 1	205	<b>0</b> 3	<b>.</b> 1_	<b>0</b> 1		
	210	Asp	TILL	Leu	гля	215	GIU	гув	Pne	PIO	220	HIS	стХ	ALA	GIA		
		Cve	Wal	Gly	Gl n		mb x	50 <b>~</b>	7 am	T ***		mb∽	Dro	Mb~	Dro		
225	Dea	Cys	var	_	230	H211	7111	SET	-	<sub>டத்</sub> 235	стА	1111	PIO	TILL	240		
	T.e.i	T.e.u	Pro	Glu		ጥሥ	<b>ም</b> ኮ ሥ	Sar			Gla	uie	<u> </u>	Glw			
<b>-</b>		100		245	1110	115			250	FIO	GIII	HTS	_	255	GLY		
Glv	His	Arσ		Gly	Phe	Pro	Glv			Glv	Δla	Ser			Glv		
<u>-</u>			260	<b>4</b> 23		110		265	ALG.	GIY .	ALC		270	ar 9	Cly		
Lvs :	Phe			Pro .	Ara	Ala			Val	Pro	Ser '			Asn	ጥህጉ		
- <u>-</u>		275	- <u>-</u>				280	- <u>,</u> -				-y- 285			-1-		
His :			Glv	Glu :	Lvs .			Glv	Ala '	Pro			Pro '	Thr	Lvs		
	290		4		-	295		4			300		_ =				

Va	l Tyr	Gly	Leu	Met	Tyr	Phe	Gly	Pro	Glu	Glu	Leu	Arg	Phe	Ser	Arg
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Th	r Trp	Ile	Gly	Ile	Trp	Ser	Val	Leu	Cys	Cys	Ala	Ser	Thr	Leu	Phe
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Ar	g Pro	Ile	Ile	Phe	Leu	Ser	Gly	Cys	Tyr	Thr	Ala	Val	Ala	Val	Ala
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ту	r Ile	Ala	Gly	Phe	Leu	Leu	Glu	Asp	Arg	Val	Val	Cys	Asn	Asp	Lys
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Ph	e Ala	Glu	Asp	Gly	Ala	Arg	Thr	Val	Ala	Gln	Gly	Thr	Lys	Lys	Glu
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Gl	у Суз	Thr	Ile	Leu	Phe	Met	Met	Leu	Tyr	Phe	Phe	Ser	Met	Ala	Sez
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Se	r Ile	Trp	Trp	Val	Ile	Leu	Ser	Leu	Thr	Trp	Phe	Leu	Ala	Ala	Gl
			420					425					430		
Me	t Lys	Trp	Gly	His	Glu	Ala	Ile	Glu	Ala	Asn	Ser	Gln	Tyr	Phe	His
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Le	u Ale	Ala	Trp	Ala	Val	Pro	Ala	Ile	Lys	Thr	Ile	Thr	Ile	Leu	Ale
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Ph	e Arg	Asp	Gln	Trp	Glu	Arg	Ser	Trp	Val	Ala	Gln	Ser	Cys	Lys	Ser
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His	Pro	Pro	Met	Ser	Pro	Asp	Phe	Thr	Val	Phe	Met	Ile	Lys	Tyr	Leu
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Lys	Thr	Leu	Asn	Ser	Trp	Arg	Lys	Phe	Tyr	Thr	Arg	Leu	Thr	Asn	Ser
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1	_			5					10	_		_1		15	
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Asn	Ala		Met	Asp	Phe	Ala		Leu	Pro	Ala	Leu		Gly	Ala	THE
_	_	35	<b>~</b> 3	<b></b> 1	•	<b>01</b> -	40	<b>5</b> \.	<b>T</b>	**-1	<b>~</b> 1	45	ui a	D=0	7 an
Leu		GIN	GIU	GIĀ	Leu		GIĀ	Pne	Leu	val	60	ALG	His	PLO	Asp
	50	<b>~</b>	0	D	71.	55 21a	77	D	D=0	Dro		Dro	Val	yan	Glv
	ATA	cys	Set	PIO	70	MIG	PIO	PLO	PIO	75	ALG	FIO	Val	131311	80
65	1701	Dho	T10	715		T All	Ara	Ara	Dhe		Cva	Δan	Phe	Asp	
261	AGT	FIIC	TTG	85	Dea	Leu	an 9	y	90	ıwp	CyD	*****		95	
Tara	17a7	T.a.ı	λan		Gln	Targ	Δla	Glv		Glv	Δla	Ala	Val		His
пуэ	Val	Den	100	ALU	<b>J</b> 211	шуз	mu	105	-1-	011			110		
Aan	Val	Asn		asn	Glu	Leu	Leu		Met.	Val	Ттт	Asn	Ser	Glu	Glu
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Tle	Gln		Gln	Ile	Tro	Ile		Ser	Val	Phe	Ile		Glu	Arq	Ser
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Ser		Tvr	Leu	Ara	Ala		Phe	Val	Tyr	Glu		Gly	Ala	Arq	Val
145		- <b>_</b> -			150				-4-	155	- 4 -			-	160

Leu	Leu	Val	. Pro	Asp	Asn	Thr	Phe	Pro	Let	ı Gly	Tyr	туз	: Let	1 Ile	Pro
				165					170	)				175	5
Phe	Thr	Gly	' Ile	Val	Gly	Leu	Leu	Val	Let	ı Ala	ı Met	Gly	, Ala	val	L Met
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Ile	Ala	Arg	Cys	Ile	Gln	His	Arg	Lys	Arg	, Leu	Gln	Arg	, Asn	Arg	Let
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Thr	Lys	Glu	Gln	Leu	Lys	Gln	Ile	Pro	Thr	His	Asp	Tyr	Gln	Lys	Gly
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Asp	Gln	Tyr	Asp	Val	Cys	Ala	Ile	Суз	Leu	Asp	Glu	Tyr	Glu	Asp	Gly
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Asp	Lys	Leu	Arg	Val	Leu	Pro	Суз	Ala	His	Ala	Tyr	His	Ser	Arg	Cys
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Val	Asp	Pro	Trp	Leu	Thr	Gln	Thr	Arg	Lys	Thr	Cys	Pro	Ile	Cys	Lys
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Phe	Gly	Ser	Leu	Ala	Pro	Ala	Pro	Leu	Val	Phe	Pro	Gly	Pro	Ser	Thr
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Val Val Tyr Gly Ser Leu Ala Leu Phe Thr Thr Ile Leu His Asn Val

Phe Leu Leu Tyr Tyr Val Asp Thr Phe Val Ser Val Tyr Lys Ile Asn

25

35

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40

45

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<b>6</b> 5					70					75					80
Ser	Gln	Pro	Arg	Gly	Arg	Asp	Leu	Pro	Trp	Leu	Gly	Leu	Val	Gly	Pro
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Ser	Gly	Leu	Trp	Thr	Ala	Asn	Thr	Leu	Суз	Суз	Phe	Trp	Lys	Ile	Pro
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Leu	Pro	His	Pro	Cys	Leu	Ser	Pro	Ser	Ser	Pro	Pro	Thr	Leu	Arg	Ser
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Tyr	Ile	Val	Ala	Gly	Val	Phe	Ile	Ala	Ile	Ser	Leu	Leu	Gln	Ile	Phe
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Val	Val	Leu	Ala	Ile	Leu	Ala	Arg	Asn	Ala	Glu	His	Ser	Leu	Pro	His
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Leu '	Tro	Cvs .	Ala	Thr .	asa	His	Asn	Val	αεA	Asn '	Thr	Thr	Glu .	Met :	Leu

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Gln	Glu	Trp	Leu	Ala	Ala	Val	Gly	Asp	Asp	Tyr	Ala	Ala	Val	Val	TI
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Arg	Pro	Glu	Gly	Glu	Pro	Arg	Phe	Tyr	Pro	Asp	Glu	Glu	Gly	Pro	Lys
			100					105					110		
His	Trp	Thr	Lys	Glu	Arg	His	Gln	Phe	Leu	Met	Glu	Leu	Lys	Gln	Glu
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Asp	Thr	Asp	Asn	Ile	Leu	Thr	Asn	Asn	Gln	Thr	Leu	Arg	Leu	Leu	Met
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Gly	Gln	Gly	Leu	Pro	Val	Val	Ala	Pro	Met	Leu	Asp	Ser	Gln	Thr	Туг
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Val	Arg	Phe	Glu	Ser	Asn	Phe	Arg	Gly	Arg	Leu	Glu	Arg	Leu	Met	Glu
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Arg	Leu	Ile	Ser	Trp	Ser	Gly	Ser	Gln	Lys	Thr	Leu	Arg	Ser	Pro	Arg
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Cys	Glu	Ser	Gly	His	Cys	Суз	Gly	Glu	Thr	Gly	Суз	Сув	Thr	Tyr	Туз
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Ala	His	Phe	Glu	Gly	Thr	Asn	Val	Glu	Gly	Val	Ser	Ser	His	Gln	Ser
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#### 14/233

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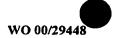
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Leu	Tyr	Thr	Val	Pro	Ala	Thr	Ile	Val	Ile	Ala	Суз	Tyr	Phe	Tyr	Glu	
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cag	gcc	ttc	cgg	gac	cag	tgg	gaa	cgc	agc	tgg	gtg	gcc	cag	agc	tgc	1910
Gln	Ala	Phe	Arg	Asp	Gln	Trp	Glu	Arg	Ser	Trp	Val	Ala	Gln	Ser	Cys	
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aag	agc	tac	gct	atc	ccc	tgc	cct	cac	ctc	cag	gcg	ggc	gga	ggc	gcc	1958
Lys	Ser	Tyr	Ala	Ile	Pro	Cys	Pro	His	Leu	Gln	Ala	Gly	Gly	Gly	Ala	
575					580					585					590	
ccg	ccg	cac	ccg	ccc	atg	agc	ccg	gac	ttc	acg	gtc	ttc	atg	att	aag	2006
Pro	Pro	His	Pro	Pro	Met	Ser	Pro	qaA	Phe	Thr	Val	Phe	Met	Ile	Lys	
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tac	ctt	atg	acg	ctg	atc	gtg	ggc	atc	acg	tcg	ggc	ttc	tgg	atc	tgg	2054
Tyr	Leu	Met	Thr	Leu	Ile	Val	Gly	Ile	Thr	Ser	Gly	Phe	Trp	Ile	Trp	
			610					615					620			
tcc	ggc	aag	acc	ctc	aac	tcc	tgg	agg	aag	ttc	tac	acg	agg	ctc	acc	2102
Ser	Gly	Lys	Thr	Leu	Asn	Ser	Trp	Arg	Lys	Phe	Tyr	Thr	Arg	Leu	Thr	
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#### 26/233

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645

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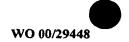
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Met His Pro Ala Ala Phe Pro Leu Pro Val Val Ala	271
1 5 10	
get gtg ctg tgg gga geg gee eeg ace egg ggg ete att ega geg ace	339
Ala Val Leu Trp Gly Ala Ala Pro Thr Arg Gly Leu Ile Arg Ala Thr	
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Gly Ala Thr Leu Ser Gln Glu Gly Leu Gln Gly Phe Leu Val Glu Ala	
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His Pro Asp Asn Ala Cys Ser Pro Ile Ala Pro Pro Pro Pro Ala Pro	
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Phe	Asp	Leu	Lys	Val	Leu	Asn	Ala	Gln	Lys	Ala	Gly	Tyr	Gly	Ala	Ala	
	95					100					105					
gta	gta	cac	aat	gtg	aat	tcc	aat	gaa	ctt	ctg	aac	atg	gtg	tgg	aat	627
Val	Val	His	Asn	<b>Val</b>	Asn	Ser	Asn	Glu	Leu	Leu	Asn	Met	Val	Trp	Asn	
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agt	gag	gaa	atc	cag	cag	cag	atc	tgg	atc	ccg	tct	gta	ttt	att	<b>9</b> 99	675
Ser	Glu	Glu	Ile	Gln	Gln	Gln	Ile	Trp	Ile	Pro	Ser	Val	Phe	Ile	Gly	
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Asn	Arg	Leu	Thr	Lys	Glu	Gln	Leu	Lys	Gln	Ile	Pro	Thr	His	Asp	Tyr	
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Glu	Asp	Gly	Asp	Lys	Leu	Arg	Val	Leu	Pro	Cys	Ala	His	Ala	Tyr	His	
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Ser	Arg	Суз	Val	Asp	Pro	Trp	Leu	Thr	Gln	Thr	Arg	Lys	Thr	Суз	Pro	
	255					260					265					

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Ile Cys Lys Gln Pro Val His Arg Gly Pro Gly Asp Glu Asp Gln Glu	
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Glu Glu Thr Gln Gly Gln Glu Gly Asp Glu Gly Glu Pro Arg Asp	
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His Pro Ala Ser Glu Arg Thr Pro Leu Leu Gly Ser Ser Pro Thr Leu	
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Val.	
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Met Cly Ten	

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Gly	Gln	Pro	Gln	Ala	Trp	Leu	Leu	Gly	Leu	Pro	Thr	Ala	Val	Val	Tyr	
	5					10					15					
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Gly	Ser	Leu	Ala	Leu	Phe	Thr	Thr	Ile	Leu	His	Asn	Val	Phe	Leu	Leu	
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Tyr	Tyr	Val	Asp	Thr	Phe	Val	Ser	Val	Tyr	Lys	Ile	Asn	Lys	Met	Ala	
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Phe	Trp	Val	Gly	Glu	Thr	Val	Phe	Leu	Leu	Trp	Asn	Ser	Leu	Asn	Asp	
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ccc	ctc	ttc	ggt	tgg	ctc	agt	gac	cgg	cag	ttc	ctc	agc	tcc	cag	ccc	478
Pro	Leu	Phe	Gly	Trp	Leu	Ser	Asp	Arg	Gln	Phe	Leu	Ser	Ser	Gln	Pro	
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								ggc								526
Arg	Gly	Arg	qaA	Leu	Pro	Trp	Leu	Gly	Leu	Val	Gly	Pro	Ser	Gly	Leu	
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		_						ttc								574
Trp	Thr	Ala	Asn.	Thr	Leu	Cys	Суз	Phe	Trp		Ile	Pro	Leu	Pro		
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Pro	Cys	Leu	Ser	Pro	Ser	Ser	Pro	Pro	Thr	Leu	Arg	Ser	Gly		Pro	
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					_			agg								670
Ile	Pro	Phe	Gly	His	Gln	Pro	Asn	Arg	Leu	Ile	Arg	Gly		Lys	Leu	
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Gly	Gln	Arg	Arg	Arg	Val	Tyr		Leu	Val	Arg	Arg		Ala	Leu	Leu	
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_								gca								766
Lys		Cys	Gly	Ala	Gly		Gly	Ala	Gly	Pro		Leu	Ala	Trp	BLA	
	165					170		4_•			175					01 /
act	act	aac	act	atc	att	cct	adc	att	cta	aat	acc	CTG	qqc	CCC	agc	814



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Trp Pro Ala Val Leu Ala Val Pro Val Pro Leu	
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chagaag and can had bee agu to good and good and good and	
Met His Tyr Tyr Arg Tyr Ser Asn Ala Lys Val Ser Cys Trp	
Met His Tyr Tyr Arg Tyr Ser Asn Ala Lys Val Ser Cys Trp 1 5 10	
Met His Tyr Tyr Arg Tyr Ser Asn Ala Lys Val Ser Cys Trp  1 5 10  tac aag tac etc ett tte age tac aac atc atc tte tgg ttg get gga	158
Met His Tyr Tyr Arg Tyr Ser Asn Ala Lys Val Ser Cys Trp  1 5 10  tac aag tac etc ett tte age tac aac atc atc tte tgg ttg get gga Tyr Lys Tyr Leu Leu Phe Ser Tyr Asn Ile Ile Phe Trp Leu Ala Gly	
Met His Tyr Tyr Arg Tyr Ser Asn Ala Lys Val Ser Cys Trp  1 5 10  tac aag tac ctc ctt ttc agc tac aac atc atc ttc tgg ttg gct gga Tyr Lys Tyr Leu Leu Phe Ser Tyr Asn Ile Ile Phe Trp Leu Ala Gly  15 20 25 30	158
Met His Tyr Tyr Arg Tyr Ser Asn Ala Lys Val Ser Cys Trp  1 5 10  tac aag tac etc ett tte age tac aac atc atc tte tgg ttg get gga Tyr Lys Tyr Leu Leu Phe Ser Tyr Asn Ile Ile Phe Trp Leu Ala Gly 15 20 25 30 gtt gte tte ett gga gte ggg etg tgg gea tgg age gaa aag ggt gtg	
Met His Tyr Tyr Arg Tyr Ser Asn Ala Lys Val Ser Cys Trp  1 5 10  tac aag tac etc ett tte age tac aac atc atc tte tgg ttg get gga Tyr Lys Tyr Leu Leu Phe Ser Tyr Asn Ile Ile Phe Trp Leu Ala Gly 15 20 25 30  gtt gte tte ett gga gte ggg etg tgg gca tgg age gaa aag ggt gtg Val Val Phe Leu Gly Val Gly Leu Trp Ala Trp Ser Glu Lys Gly Val	158
Met His Tyr Tyr Arg Tyr Ser Asn Ala Lys Val Ser Cys Trp  1 5 10  tac aag tac etc ett tte age tac aac atc atc tte tgg ttg get gga Tyr Lys Tyr Leu Leu Phe Ser Tyr Asn Ile Ile Phe Trp Leu Ala Gly 15 20 25 30  gtt gtc tte ett gga gte ggg etg tgg gca tgg age gaa aag ggt gtg Val Val Phe Leu Gly Val Gly Leu Trp Ala Trp Ser Glu Lys Gly Val  35 40 45	158 206
Met His Tyr Tyr Arg Tyr Ser Asn Ala Lys Val Ser Cys Trp  1 5 10  tac aag tac ctc ctt ttc agc tac aac atc atc ttc tgg ttg gct gga Tyr Lys Tyr Leu Leu Phe Ser Tyr Asn Ile Ile Phe Trp Leu Ala Gly 15 20 25 30  gtt gtc ttc ctt gga gtc ggg ctg tgg gca tgg agc gaa aag ggt gtg Val Val Phe Leu Gly Val Gly Leu Trp Ala Trp Ser Glu Lys Gly Val  35 40 45  ctg tcc gac ctc acc aaa gtg acc cgg atg cat gga atc gac cct gtg	158
Met His Tyr Tyr Arg Tyr Ser Asn Ala Lys Val Ser Cys Trp  1 5 10  tac aag tac etc ett tte age tac aac atc atc tte tgg ttg get gga Tyr Lys Tyr Leu Leu Phe Ser Tyr Asn Ile Ile Phe Trp Leu Ala Gly 15 20 25 30  gtt gte tte ett gga gte ggg etg tgg gca tgg age gaa aag ggt gtg Val Val Phe Leu Gly Val Gly Leu Trp Ala Trp Ser Glu Lys Gly Val  35 40 45  etg tee gae etc ace aaa gtg ace egg atg eat gga ate gae ect gtg Leu Ser Asp Leu Thr Lys Val Thr Arg Met His Gly Ile Asp Pro Val	158 206
Met His Tyr Tyr Arg Tyr Ser Asn Ala Lys Val Ser Cys Trp  1 5 10  tac aag tac ctc ctt ttc agc tac aac atc atc ttc tgg ttg gct gga Tyr Lys Tyr Leu Leu Phe Ser Tyr Asn Ile Ile Phe Trp Leu Ala Gly 15 20 25 30  gtt gtc ttc ctt gga gtc ggg ctg tgg gca tgg agc gaa aag ggt gtg Val Val Phe Leu Gly Val Gly Leu Trp Ala Trp Ser Glu Lys Gly Val  35 40 45  ctg tcc gac ctc acc aaa gtg acc cgg atg cat gga atc gac cct gtg Leu Ser Asp Leu Thr Lys Val Thr Arg Met His Gly Ile Asp Pro Val 50 55 60	158 206 254
Met His Tyr Tyr Arg Tyr Ser Asn Ala Lys Val Ser Cys Trp  1 5 10  tac aag tac ctc ctt ttc agc tac aac atc atc ttc tgg ttg gct gga Tyr Lys Tyr Leu Leu Phe Ser Tyr Asn Ile Ile Phe Trp Leu Ala Gly 15 20 25 30  gtt gtc ttc ctt gga gtc ggg ctg tgg gca tgg agc gaa aag ggt gtg Val Val Phe Leu Gly Val Gly Leu Trp Ala Trp Ser Glu Lys Gly Val  35 40 45  ctg tcc gac ctc acc aaa gtg acc cgg atg cat gga atc gac cct gtg Leu Ser Asp Leu Thr Lys Val Thr Arg Met His Gly Ile Asp Pro Val  50 55 60  gtg ctg gtc ctg gtg gtg gtg gtg atg ttc acc ctg ggg ttc gcc	158 206
Met His Tyr Tyr Arg Tyr Ser Asn Ala Lys Val Ser Cys Trp  1 5 10  tac aag tac ctc ctt ttc age tac aac atc atc ttc tgg ttg gct gga Tyr Lys Tyr Leu Leu Phe Ser Tyr Asn Ile Ile Phe Trp Leu Ala Gly 15 20 25 30  gtt gtc ttc ctt gga gtc ggg ctg tgg gca tgg agc gaa aag ggt gtg Val Val Phe Leu Gly Val Gly Leu Trp Ala Trp Ser Glu Lys Gly Val  ctg tcc gac ctc acc aaa gtg acc cgg atg cat gga atc gac cct gtg Leu Ser Asp Leu Thr Lys Val Thr Arg Met His Gly Ile Asp Pro Val  50 55 60  gtg ctg gtc ctg atg gtg gtg gtg atg ttc acc ctg ggg ttc gcc Val Leu Val Leu Met Val Gly Val Val Met Phe Thr Leu Gly Phe Ala	158 206 254
Met His Tyr Tyr Arg Tyr Ser Asn Ala Lys Val Ser Cys Trp  1 5 10  tac aag tac ctc ctt ttc agc tac aac atc atc ttc tgg ttg gct gga Tyr Lys Tyr Leu Leu Phe Ser Tyr Asn Ile Ile Phe Trp Leu Ala Gly 15 20 25 30  gtt gtc ttc ctt gga gtc ggg ctg tgg gca tgg agc gaa aag ggt gtg Val Val Phe Leu Gly Val Gly Leu Trp Ala Trp Ser Glu Lys Gly Val  35 40 45  ctg tcc gac ctc acc aaa gtg acc cgg atg cat gga atc gac cct gtg Leu Ser Asp Leu Thr Lys Val Thr Arg Met His Gly Ile Asp Pro Val  50 55 60  gtg ctg gtc ctg atg gtg ggc gtg gtg atg ttc acc ctg ggg ttc gcc Val Leu Val Leu Met Val Gly Val Val Met Phe Thr Leu Gly Phe Ala 65 70 75	158 206 254 302
Met His Tyr Tyr Arg Tyr Ser Asn Ala Lys Val Ser Cys Trp  1 5 10  tac aag tac etc ett tte age tac aac atc atc tte tgg ttg get gga Tyr Lys Tyr Leu Leu Phe Ser Tyr Asn Ile Ile Phe Trp Leu Ala Gly 15 20 25 30  gtt gtc tte ett gga gte ggg etg tgg gca tgg age gaa aag ggt gtg Val Val Phe Leu Gly Val Gly Leu Trp Ala Trp Ser Glu Lys Gly Val  35 40 45  etg tce gae etc acc aaa gtg acc egg atg eat gga atc gae ect gtg Leu Ser Asp Leu Thr Lys Val Thr Arg Met His Gly Ile Asp Pro Val 50 55 60  gtg etg gte etg atg gtg gge gtg gtg atg tte acc etg ggg tte gee Val Leu Val Leu Met Val Gly Val Val Met Phe Thr Leu Gly Phe Ala 65 70 75  gge tge gtg gtg gtg gtg atg tte etc aac ttt aac	158 206 254
Met His Tyr Tyr Arg Tyr Ser Asn Ala Lys Val Ser Cys Trp  1 5 10  tac aag tac ctc ctt ttc agc tac aac atc atc ttc tgg ttg gct gga Tyr Lys Tyr Leu Leu Phe Ser Tyr Asn Ile Ile Phe Trp Leu Ala Gly 15 20 25 30  gtt gtc ttc ctt gga gtc ggg ctg tgg gca tgg agc gaa aag ggt gtg Val Val Phe Leu Gly Val Gly Leu Trp Ala Trp Ser Glu Lys Gly Val  35 40 45  ctg tcc gac ctc acc aaa gtg acc cgg atg cat gga atc gac cct gtg Leu Ser Asp Leu Thr Lys Val Thr Arg Met His Gly Ile Asp Pro Val  50 55 60  gtg ctg gtc ctg atg gtg ggc gtg gtg atg ttc acc ctg ggg ttc gcc Val Leu Val Leu Met Val Gly Val Val Met Phe Thr Leu Gly Phe Ala 65 70 75	158 206 254 302

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30 35 40

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His	s Se	r Lei	ı Pro	His	з Ту	Let	ı Gly	, Ala	a Let	ı Glı	ı Ar	g Le	u As <sub>j</sub>	р Ту	r Pro	
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Ala	Ala	Val			Arg	Pro	Glu	Gly	Glu	Pro	Arg	Phe	Туг	Pro	qeA o	
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GIU	GIU			Lys	Hls	Trp			Glu	Arg	His			Lev	Met	
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GIU	125		GIII	GIU	MLa	130	TILL	Pne	ATA	Arg	Asn 135	Trp	о Сту	ALS	Asp	
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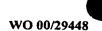
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cgt	tta	act	ggc	gac	tcc	ggt	att	gag	ctc	tgc	cct	tgt	cct	gcc	tcc	677	
Arg	Leu	Thr	Gly	Asp	Ser	Gly	Ile	Glu	Leu	Cys	Pro	Cys	Pro	Ala	Ser		
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Gly	Glu	Gly	Glu	Pro	Val	Lys	Glu	Val	Arg	Val	Ser	Ala	Thr	Leu	Pro		
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gat	ctg	gag	gac	tac	tcc	ccg	tgt	gca	cta	ccc	cca	gag	tct	gta	ccg	773	
Asp	Leu	Glu	Asp	Tyr	Ser	Pro	Cys	Ala	Leu	Pro	Pro	Glu	Ser	Val	Pro		
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cag	atc	ttt	ccc	atg	<b>9</b> 99	ctg	tct	tcc	agt	gaa	ggg	gac	atc	cca		818	
Gln	Ile	Phe	Pro 1	Met	Gly	Leu	Ser	Ser	Ser	Glu	Gly	Asp	Ile	Pro			
250					255					260							
ta a	igtag	tttt	g ag	aggg	tgga	tgg	gtta	ctt	gccc	acca	ga a	acag	rcect	a		870	

PCT/JP99/06412

gtoccaacto ottgogttoo tttggoccot cootgoctac otagaatotg cotgaaaggg	930
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Asp Cys Leu Arg Asp Trp Glu Asp Leu Gln Gln Asp Phe Gln Asn Ile	
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Gln Glu Thr His Arg Leu Tyr Arg Leu Lys Leu Glu Glu Leu Thr Lys	
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Leu Gln Asn Asn Cys Thr Ser Ser Ile Thr Arg Gln Lys Lys Arg Leu	
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cag gag ctg gcc ctc gcc ctg aag aaa tgc aaa ccc tcc ctc cca gca	245
Gln Glu Leu Ala Leu Ala Leu Lys Lys Cys Lys Pro Ser Leu Pro Ala	
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gag gee gag ggg gee gea eag gag etg gag aac eag atg aaa gag ege	293
Glu Ala Glu Gly Ala Ala Glu Glu Leu Glu Asn Gln Met Lys Glu Arg	
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Gln Gly Leu Phe Phe Asp Met Glu Ala Tyr Leu Pro Lys Lys Asn Gly	
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ttg tac ctg age ctg gtt ctg ggg aac gtc aac gtc acg ctc ctg age	389
Leu Tyr Leu Ser Leu Val Leu Gly Asn Val Asn Val Thr Leu Leu Ser	



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Lys	Glr	Ala	Lys	Phe	Ala	Туг	Lys	Asp	Glu	1 Туг	: Glu	ı Lys	Phe	∋ Ly:	s Leu	
		125	<b>j</b>				130	)				135	5			
tac	cto	acc	ato	ato	cto	ato	ctc	ato	tec	tto	act	tgo	e ego	tto	ctg	485
Tyr	Leu	Thr	Ile	lle	Lev	Ile	Leu	Ile	e Ser	Phe	Thi	Cys	Arg	y Phe	e Leu	
	140	)				145	i				150	)				
ctc	aac	tco	agg	gtg	aca	gat	gct	gco	tto	aac	tto	cto	cto	gto	tgg	533
Leu	Asn	Ser	Arg	Val	Thr	Asp	Ala	Ala	Phe	Asn	Phe	Lev	Lev	val	Trp	
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Tyr	Tyr	Cys	Thr	Leu	Thr	Ile	Arg	Glu	Ser	Ile	Leu	Ile	Asn	Asn	Gly	
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tee	cgg	atc	aaa	ggc	tgg	tgg	gtg	ttc	cat	cac	tac	gtg	tcc	acc	ttc	629
Ser	Arg	Ile	Lys	Gly	Trp	Trp	Val	Phe	His	His	Tyr	Val	Ser	Thr	Phe	
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Leu	Ser		Val	Met	Leu	Thr	Trp	Pro	Asp	Gly	Leu	Met	Tyr	Gln	Lys	
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Phe		Asn	Gln	Phe	Leu	_	Phe	Ser	Met	Tyr			Phe	Val	Gln	•
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	Leu	Gln	Tyr	Tyr		Gln	Ser	Gly	Cys		Tyr	Arg	Leu	Arg		
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						_	_		act					_		821
Leu	GIY	GIU	Arg		ınr	Met	Asp	Leu	Thr	Val	Giu	GIY	Pne		Ser	
<b>-</b> ~~	a+#	<b>+</b>		255					260				<b></b>	265		969
				_				_	ctg							869
тъ	Het	пр	270	GIÀ	ren	Thr	Pne		Leu	Pro	Pne	Leu	280	Pne	GTÅ	
220	++-	+~~		a++	+++			275								017
							-	-	acg Thr	_			_	_	_	917
		285		u	~ .16	-1011	290	acu.	T11T	⊒e'u	E116	295	Litt	A.C	3111	
ac.	cct		tơc	aac	aaa	taa		ata	ctt	ato	tac		ttt	CCC	ttc	965

Asp Pro Gin Cys Lys Giu Trp Gin Vai Leu Met Cys Giy Phe Pro Phe	
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Leu Leu Phe Leu Gly Asn Phe Phe Thr Thr Leu Arg Val Val His	
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cac aag ttt cac agt cag cgg cac ggg agc aag aag gat tgaggctg	1060
His Lys Phe His Ser Gln Arg His Gly Ser Lys Lys Asp	
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Leu Leu Gln Leu Leu Val Leu Leu Leu Thr Leu Pro Leu His Leu Met	
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Ala Leu Leu Gly Cys Trp Gln Pro Leu Cys Lys Ser Tyr Phe Pro Tyr	
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Leu Met Ala Val Leu Thr Pro Lys Ser Asn Arg Lys Met Glu Ser Lys	
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Lys Arg Glu Leu Phe Ser Gln Ile Lys Gly Leu Thr Gly Ala Ser Gly	
55 50 65 70	

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Phe	Tyr	Pro	Pro	Gly	Суз	Arg	Val	Thr	Cys	Leu	Asp	Pro	Asn	Pro	His	
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Phe	Glu	Lys	Phe	Leu	Thr	Lys	Ser	Met	Ala	Glu	Asn	Arg	His	Leu	Gln	
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tat	gag	cgg	ttt	gtg	gtg	gct	cct	gga	gag	gac	atg	aga	cag	ctg	gct	440
Tyr	Glu	Arg	Phe	Val	Val	Ala	Pro	Gly	Glu	Asp	Met	Arg	Gln	Leu	Ala	
	120					125					130					
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Asp	Gly	Ser	Met	Asp	Val	Val	Val	Cys	Thr	Leu	Val	Leu	Cys	Ser	Val	
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Gln	Ser	Pro	Arg	Lys	Val	Leu	Gln	Glu	Val	Arg	Arg	Val	Leu	Arg	Pro	
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Gly	Gly	Val	Leu	Phe	Phe	Trp	Glu	His	Val	Ala	Glu	Pro	Tyr	Gly	Ser	
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rp	Ala		Met	Trp	Gln	Gln		Phe	Glu	Pro	Thr	Trp	Lys	His	Ile	
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	GIN	Phe	Ser			Gln	Met	Glu	-		Pro	Pro	Pro		_	
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rp !	Leu .	Pro			Pro	His	Ile	Met	_	Lys	Ala	Val	Lys			
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1gcc1	catc	ta t	CTTC	cact	g ag	aggg	acct	agc	agaa	tga	gaga	agac	at t	catg	tacca	900

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Ala Leu Val Gln Leu Gly Gln Pro Cys Asp Cys Leu Pro Pro Leu Arg	,
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Ala Ala Ala Glu Gln Leu Arg Gln Lys Asp Leu Arg Ile Ser Gln Leu	
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caa geg gaa ete ega egg eea eee eet gee eet gee eag eee eet gaa	
Sin Ala Glu Leu Arg Arg Pro Pro Pro Ala Pro Ala Gin Pro Pro Glu	
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ecc gag gcc ctg cct act atc tat gtt gtt acc ccc acc tat gcc agg	295
	295

CCC	: cto	, tg	ggt	g cag	tac	cct	cag	gat	gtg	act	aco	tto	aat	t at	a gat	34	3
Pro	Lev	Tr	Va]	l Glm	Туг	Pro	Gln	Asp	Val	. Thi	Thi	Phe	Ası	n Ile	qaA s		
			90	)				95					10	כ			
gat	cag	tac	ttg	g ctt	ggg	gat	geg	ttg	ctg	gtt	cac	cct	gta	a to	a gac	39	1
Asp	Gln	тут	Lev	ı Leu	Gly	qaA	Ala	Leu	Leu	Val	. His	Pro	Va]	L Se	c Asp		
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Ser	Gly	Ala	His	Gly	Val	Gln	Val	Tyr	Leu	Pro	Gly	Gln	Gly	g Glu	val		
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Trp	Tyr	Asp	Ile	Gln	Ser	Tyr	Gln	Lys	His	His	Gly	Pro	Gln	Thi	Leu		
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Tyr	Leu	Pro	Val	Thr	Leu	Ser	Ser	Ile	Pro	Val	Phe	Gln	Arg	Gly	Gly		
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aca	atc	gtg	cct	cga	tgg	atg	cga	gtg	cgg	cgg	tct	tca	gaa	tgt	atg	583	3
Thr	Ile	Val	Pro	Arg	Trp	Met	Arg	Val	Arg	Arg	Ser	Ser	Glu	Cys	Met		
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Lys	Asp	Asp	Pro	Ile	Thr	Leu	Phe	Val	Ala	Leu	Ser	Pro	Gln	Gly	Thr		
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Ala	Gln	Gly	Glu	Leu	Phe	Leu	Asp	Asp	Gly	His	Thr	Phe	Asn	Tyr	Gln		
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Chr	Arg	Gln	Glu	Phe	Leu	Leu	Arg	Arg	Phe	Ser	Phe	Ser	Gly	Asn	Thr		
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eu	Val	Ser	Ser	Ser	Ala	Asp	Pro	Glu	Gly	His	Phe	Glu	Thr	Pro	Ile		
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			250					255					260				
rta	ctc	cag	aca	aaa	gga	tct	cca	gaa	agc	cgc	ctg	tcc	ttc	cag	cat	871	
7a]	ום.ז	G) n	መኮሎ	Tazo	G) v	S02	Dro	G) 11	Sor	<b>&gt;</b>	T 011	Sar	Dho	Gln.	ui a		

265	270	275	
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Asp Pro Glu Thr Ser Va	ıl Leu Val Leu A	Arg Lys Pro Gly Ile As	n Val
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Ala Ser Asp Trp Ser Il	e His Leu Arg		
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			M	let A	sp L	ys I	eu L	ys L	ys V	al I	eu S	er G	ly (	ln A	sp T	hæ	
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gag	gac	cgg	agc	ggc	ctg	tcc	gag	gtt	gtt	gag	gca	tct	tca	tta	agc	15	9
Glu	Asp	Arg	Ser	Gly	Leu	Ser	Glu	Val	Val	Glu	Ala	Ser	Ser	Let	Ser		
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Trp	Ser	Thr	Arg	Ile	Lys	Gly	Phe	Ile	Ala	Cys	Phe	Ala	Ile	Gly	Ile		
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Leu	Cys	Ser	Leu	Leu	Gly	Thr	Val	Leu	Leu	Trp	Val	Pro	Arg	Lys	Gly		
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Leu	His	Leu	Phe	Ala	Val	Phe	Tyr	Thr	Phe	Gly	Asn	Ile	Ala	Ser	Ile		
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Phe	Glu	Pro	Thr	Arg	Leu	Ile	Ala	Thr	Ile	Met	Val	Leu	Leu	Cys	Phe		
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Leu	Ile	Phe	Суз	Ile	Leu	Gln	Ser	Leu	Ala	Leu	Thr	Trp	Tyr	Ser	Leu		
				130					135					140			
tcc	ttc	ata	cca	ttt	gca	agg	gat	gct	gtg	aag	aag	tgt	ttt	gcc	gtg	543	,
Ser :	Phe	Ile	Pro	Phe	Ala	Arg	Asp	Ala	Val	Lys	Lys	Cys	Phe	Ala	Va1		
			145					150					155				
tgt (	ctt	gca	taat	tcat	gg c	cagt	ttta	t ga	agct	ttgg	aag	gcac	tat	ggac	agaa	600	)
Cys :	Leu .	Ala															
		160															
			-	-			_			_		_	_	-	tttt		
cett	gcag	ca a	tgtg	ttgc	t tg	tgat	tcga	aca	tttg	agg	gtta	cttt	tg g	aago	aacaa	a 720	
- 808	-+	~~ =	east.	asat.	~ +~	- <del></del> -	aasa	800	a+~a	~~~	~+ ~~	~++ <i>~</i>	+~+	-+-+	+-+	- 790	

840 900

960

1020 1080 1124

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Thr Ala Ala Leu Ala Val Ala Pro Gly Pro Arg Phe Leu Val Thr Ala
20 25 30
Pro Gly Ile Ile Arg Pro Gly Gly Asn Val Thr Ile Gly Val Glu Leu
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Leu Glu His Cys Pro Ser Gln Val Thr Val Lys Ala Glu Leu Leu Lys
50 55 60
Thr Ala Ser Asn Leu Thr Val Ser Val Leu Glu Ala Glu Gly Val Phe
65 70 75 80
Glu Lys Gly Ser Phe Lys Thr Leu Thr Leu Pro Ser Leu Pro Leu Asn
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Ser Ala Asp Glu Ile Tyr Glu Leu Arg Val Thr Gly Arg Thr Gln Asp
100 105 110
Glu Ile Leu Phe Ser Asn Ser Thr Arg Leu Ser Phe Glu Thr Lys Arg
115 120 125
Ile Ser Val Phe Ile Gln Thr Asp Lys Ala Leu Tyr Lys Pro Lys Gln
130 135 140
Glu Val Lys Phe Arg Ile Val Thr Leu Phe Ser Asp Phe Lys Pro Tyr
145 150 155 160
Lys Thr Ser Leu Asn Ile Leu Ile Lys Asp Pro Lys Ser Asn Leu Ile
165 170 175
Gln Gln Trp Leu Ser Gln Gln Ser Asp Leu Gly Val Ile Ser Lys Thr

			180	)				185	5				190	)	
Phe	Glr	Lev	ı Ser	Sei	: His	Pro	o Ile	Let	ı Gly	/ Asp	Tr	Sea	: Ile	Gli	val
		195	5				200	)				205	5		
Gln	Val	. Asr	Asp	Glr	Thr	Туз	Tyr	Glr	sei	: Phe	Glr	val	Ser	Glu	тул
	210	)				215	5				220	)			
Val	Leu	Pro	Lys	Phe	e Glu	Va]	Thr	Leu	ı Glr	Thr	Pro	Lev	туг	Cys	Sei
225	i				230	)				235					240
Met	Asn	Ser	Lys	His	Leu	Asr	Gly	Thr	: Ile	Thr	Ala	Lys	Туг	Thr	Туг
				245	i				250	)				255	•
Gly	Lys	Pro	Val	. Lys	Gly	Asp	Val	Thr	Leu	Thr	Phe	Leu	Pro	Leu	Ser
			260	)				265	i				270		
Phe	Trp	Gly	Lys	Lys	Lys	Asn	Ile	Thr	Lys	Thr	Phe	Lys	Ile	Asn	Gly
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Ser	Ala	Asn	Phe	Ser	Phe	Asn	Asp	Glu	Glu	Met	Lys	Asn	Val	Met	Asp
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Val	Glu	Ile	Leu	Thr	Thr	Val	Thr	Glu	Ser	Val	Thr	Gly	Ile	Ser	Arg
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Thr	Val	Lys	Val	Thr	Arg	Ala	Asp	Gly	Asn	Gln	Leu	Thr	Leu	Glu	Glu
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Pro	Ile		Glu	Ąsp	Ser	Ser		Leu	Gln	Leu	Lys		Tyr	Phe	Leu
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Gly			Ser							Leu	Phe	Lys	Ser	Pro	Ser
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Asp	Val	Leu	Lys	Ile	Pro	Val	Gln	Leu	Val	Phe	Lys	Asn	Lys	Ile	Lys
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Leu	Tyr	Trp	Ser	Lys	Val	Lys	Ala	Glu	Pro	Ser	Glu	Lys	Val	Ser	Leu
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Asp	Lys	Ser	Val	Asn	Leu	Met	Asn	Ala	Ser	Asn	Asp	Ile	Thr	Met	Glu
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Asn	Val	Val	His	Glu	Leu	Glu	Leu	Tyr	Asn	Thr	Gly	Tyr	Tyr	Leu	Gly
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Met	Phe	Met	Asn	Ser	Phe	Ala	Val	Phe	Gln	Glu	Cys	Gly	Leu	Trp	Val
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Leu	Thr	qzA	Ala	Asn	Leu	Thr	Lys	Asp	Tyr	Ile	qzA	Gly	Val	Tyr	Asp
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Asn	Ala	Glu	Tyr	Ala	Glu	Arg	Phe	Met	Glu	Glu	Asn	Glu	Gly	His	Ile
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Val	Asp	Ile	His	Ązp	Phe	Ser	Leu	Gly	Ser	Ser	Pro	His	Val	Arg	ГÀа
		675					680					685			
Hìs	Phe	Pro	Glu	Thr	Trp	Ile	Trp	Leu	Asp	Thr	Asn	Met	Gly	Ser	Arg
	690					695					700				
Ile	Tyr	Gln	Glu	Phe	Glu	Val	Thr	Val	Pro	Asp	Ser	Ile	Thr	Ser	Trp
705					710					715					720
Val	Ala	Thr	Gly	Phe	Val	Ile	Ser	Glu	Asp	Leu	Gly	Leu	Gly	Leu	Thr
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ምክተ	Thr	Pro	Val	Glu	Leu	Gln	Ala	Phe	Gln	Pro	Phe	Phe	Ile	Phe	Leu

			740	0				745	;				750	)	
Ası	ı Le	ı Pro	э Туг	r Sei	. Val	. Ile	Arg	Gly	Glu	ı Glu	. Phe	Ala	Let	ı Glu	Ile
		75	5				760	)				765	i		
Thi	: Ile	Phe	e Ası	туг	Leu	Lys	Asp	Ala	Thr	Glu	Val	Lys	Val	. Ile	Ile
	770	)				775	•				780	)			
Glu	ı Lys	Sez	: Asp	Lys	Phe	Asp	Ile	Leu	Met	Thr	Ser	Ser	Glu	Ile	Asn
785	<b>;</b>				790					795					800
Ala	Thr	Gly	, His	Gln	Gln	Thr	Leu	Leu	Val	Pro	Ser	Glu	Asp	Gly	Ala
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Thr	Val	. Let	Phe	Pro	Ile	Arg	Pro	Thr	His	Leu	Gly	Glu	Ile	Pro	Ile
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Thr	Val	. Thr	Ala	Leu	Ser	Pro	Thr	Ala	Ser	Asp	Ala	Ile	Thr	Gln	Met
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Ile			Lys	Ala	Glu		Ile	Glu	Lys	Ser	Tyr	Ser	Gln	Ser	Ile
	850					855					860				
		Asp	Leu	Thr	Asp	Asn	Arg	Leu	Gln	Ser	Thr	Leu	Lys	Thr	Leu
865		_			870					875					880
Ser	Phe	Ser	Phe		Pro	Asn	Thr	Val		Gly	Ser	Glu	Arg		Gln
-1.	<b>~</b> 1			885			_		890	_				895	
тте	Thr	Ala			Asp	Val	Leu	_	Pro	Ser	Ile	Asn	_	Leu	Ala
S	T	Tla	900		Desc	<b>~</b>	<b>a</b> 1	905	<b>01</b>	<b>6</b> 3	<b>a</b> 1	•	910		_
Ser	reu	915	Arg	Met	Pro	ıyr		Cys	GTĀ	GIU	Gin		Met	шe	Asn
Dhe	λla		Aen	Tle	Tyr	T10	920	2	<i>(</i> ()	T 011	mb	925	T	T	<b>a</b> 1-
2110	930	110	ASII	116	-7-	935	Ten	Asp	TÄT	Leu	940	тÀя	тÃя	гуз	GIII
Leu		Asp	Asn	Leu	Lys		Lvs	Δla	T.e.ii	Ser		Mot	Ara	Gln	Glv
945					950		_,_	1114	Dog	955	+ 110	1100	9		960
	Gln	Arg	Glu	Leu	Leu	Tvr	Gln	Ara	Glu		Glv	Ser	Phe		
•		_		965					970		1			975	
Phe	Gly	Asn	Tyr	Asp	Pro	Ser	Gly			Trp	Leu	Ser .			Val
	_		980	-				985		-			990		
Leu	Arg	Суз	Phe	Leu	Glu	Ala	Asp	Pro	Tyr	Ile	Asp	Ile :	qeA	Gln :	Asn
	_	995					1000		_		_	1005	•		
Val	Leu	His	Arg	Thr	Tyr	Thr	Trp	Leu	Lys	Gly			Lys	Ser 2	Asn
	1010					1015			_		1020		_		

Gly Glu	Phe	Trp	Ąsp	Pro	Gly	Arg	Val	Ile	His	Ser	Glu	Leu	Gln	Gly
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Gly Asn	Lys	Ser	Pro	Val	Thr	Leu	Thr	Ala	Tyr	Ile	Val	Thr	Ser	Leu
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Leu Gly	Tyr	Arg	Lys	Tyr	Gln	Pro	Asn	Ile	Asp	Val	Gln	Glu	Ser	Ile
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His Phe	Leu	Glu	Ser	Glu	Phe	Ser	Arg	Gly	Ile	Ser	Asp	Asn	Tyr	Thr
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Leu Ala	Leu	Ile	Thr	Tyr	Ala	Leu	Ser	Ser	Val	Gly	Ser	Pro	Lys	Ala
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Lys Glu	Ala	Leu	Asn	Met	Leu	Thr	Trp	Arg	Ala	Glu	Gln	Glu	Gly	Gly
1105				1110	0				111	5				1120
Met Gln	Phe	Trp	Val	Ser	Ser	Glu	Ser	Lys	Leu	Ser	Asp	Ser	Trp	$\mathbf{Gl} \boldsymbol{v}$
			1125	5				1130	)				1135	5
Pro Arg	Ser	Leu	Asp	Ile	Glu	Val	Ala	Ala	Tyr	Ala	Leu	Leu	Ser	His
		1140	)				1145	5				1150	)	
Phe Leu	Gln	Phe	Gln	Thr	Ser	Glu	Gly	Ile	Pro	Ile	Met	Arg	Trp	Leu
	1155	5				1160	)				1165	5		
Ser Arg	Gln	Arg	Asn	Ser	Leu	Gly	Gly	Phe	Ala	Ser	Thr	Gln	Asp	Thr
1170	)				1175	5				1180	)			
Thr Val	Ala	Leu	Lys	Ala	Leu	Ser	Glu	Phe	Ala	Ala	Leu	Met	Asn	Thr
1185				1190	)				1195	5				1200
Glu Arg	Thr	Asn	Ile	Gln	Val	Thr	Val	Thr	Gly	Pro	Ser	Ser	Pro	Ser
			1205	<b>j</b>				1210	)				1215	;
Pro Val	Lys	Phe	Leu	Ile	Asp	Thr	His	Asn	Arg	Leu	Leu	Leu	Gln	Thr
		1220	)				1225	5				1230	)	
Ala Glu	Leu	Ala	Val	Val	Gln	Pro	Thr	Ala	Val	Asn	Ile	Ser	Ala	Asn
	1235	5				1240	)				1245	<b>j</b>		
Gly Phe	Gly	Phe	Ala	Ile	Cys	Gln	Leu	Asn	Val	Val	Tyr	Asn	Val	Lys
1250	)				1255	5				1260	)			
Ala Ser	Gly	Ser	Ser	Arg	Arg	Arg	Arg	Ser	Ile	Gln	Asn	Gln	Glu	Ala
1265				1270	)				1275	<b>j</b>				1280
Phe Asp	Leu	Asp	Val	Ala	Val	Lys	Glu	Asn	Lys	Asp	Asp	Leu	Asn	His
			1285	;				1290	)				1295	
Val Asp	Leu	Asn	Val	Cys	Thr	Ser	Phe	Ser	Gly	Pro	Gly	Arg	Ser	Gly

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		131	5				132	0				132	5		
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His	His	Ser	Ser	Val	Ile	Phe	Ile	Phe	Cys	Phe	Lys	Leu	Leu	Tyr	Phe
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Arg	Ala	Ser	Pro	Ala	Gly	Gly	Pro	Leu	Glu	Asp	Val	Val	Ile	Glu	Arg
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Tyr	His	Ile	Pro	Arg	Ala	Cys	Pro	Arg	Glu	Val	Gln	Met	Gly	Asp	Phe
	50					55					60				
Val	Arg	Tyr	His	Tyr	Asn	Gly	Thr	Phe	Glu	Asp	Gly	ГЛЗ	Lys	Phe	Asp
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Ser	Ser	Tyr	Asp	Arg	Asn	Thr	Leu	Val	Ala	Ile	Val	Val	Gly	Val	Gly
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Arg	Leu	Ile	Thr	Gly	Met	Asp	Arg	Gly	Leu	Met	Gly	Met	Cys	Val	Asn
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Glu	Arg	Arg	Arg	Leu	Ile	Val	Pro	Pro	His	Leu	Gly	Tyr	Gly	Ser	Ile
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Gly	Leu	Ala	Gly	Leu	Ile	Pro	Pro	Asp	Ala	Thr	Leu	Tyr	Phe	Asp	Val
	130					135					140				
Val	Leu	Leu	Asp	Val	Trp	Asn	Lys	Glu	Asp	Thr	Val	Gln	Val	Ser	Thr
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Leu	Leu	Arg	Pro	Pro	His	Суз	Pro	Arg	Met	Val	Gln	Asp	Gly	Asp	Phe
				165					170					175	
Val	Arg	Tyr	His	Tyr	Asn	Gly	Thr	Leu	Leu	Asp	Gly	Thr	Ser	Phe	Asp
			180					185					190		
Thr	Ser	Tyr	Ser	Lys	Gly	Gly	Thr	Tyr	Asp	Thr	Tyr	Val	Gly	Ser	Gly
		195					200					205			
Trp	Leu	Ile	Lys	Gly	Met	Asp	Gln	Gly	Leu	Leu	Gly	Met	Суз	Pro	Gly
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Gly	Tyr	Gly	Thr	Val	Ile	Pro	Pro	Gln	Ala	Ser	Leu	Val	Phe	His	Val
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Ser	Ser	Tyr	Ser	Arg	Asn	His	Thr	Tyr	Asn	Thr	Tyr	Ile	Gly	Gln	Gly
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Tyr	Ile	Ile	Pro	Gly	Met	Asp	Gln	Gly	Leu	Gln	Gly	Ala	Cys	Met	Gly
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Glu	Arg	Arg	Arg	Ile	Thr	Ile	Pro	Pro	His	Leu	Ala	Tyr	Gly	Glu	Asn
			340					345					350		
Gly	Thr	Gly	Asp	Lys	Ile	Pro	Gly	Ser	Ala	Val	Leu	Ile	Phe	Asn	Val

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		35	5				360	)				365	5		
His	Val	. Ile	e Asr	Phe	e His	Ası	Pro	Ala	a Asp	Va]	. Val	. Glu	ı Ile	Arc	Thr
	370	)				375	<b>5</b>				380	)			
Lev	Ser	Arg	g Pro	Ser	Glu	Thr	Cys	Asr	Glu	Thr	Thr	Lys	Lev	Gly	Asp
385	i				390	)				395					400
Phe	Val	Arg	Tyr	His	туг	Asr	Cys	Ser	Leu	Leu	Asp	Gly	Thr	Gln	Leu
				405	•				410					415	
Phe	Thr	Ser	His	Asp	тут	Gly	Ala	Pro	Gln	Glu	Ala	Thr	Leu	Gly	Ala
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Asn	Lys	Val	Ile	Glu	Gly	Leu	Asp	Thr	Gly	Leu	Gln	Gly	Met	Суз	Val
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Gly	Glu	Arg	Arg	Gln	Leu	Ile	Val	Pro	Pro	His	Leu	Ala	His	Gly	Glu
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Ser	Gly	Ala	Arg	Gly	Val	Pro	Gly	Ser	Ala	Val	Leu	Leu	Phe	Glu	Val
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Glu	Leu	Val	Ser	Arg	Glu	Asp	Gly	Leu	Pro	Thr	Gly	Tyr	Leu	Phe	Val
				485					490					495	
Trp	His	Lys	Asp	Pro	Pro	Ala	Asn	Leu	Phe	Glu	Asp	Met	Asp	Leu	Asn
			500					505					510		
Lys	Asp		Glu	Val	Pro	Pro	Glu	Glu	Phe	Ser	Thr	Phe	Ile	Lys	Ala
		515					520					525			
Gln		Ser	Glu	Gly	Lys		Arg	Leu	Met	Pro	Gly	Gln	Asp	Pro	Glu
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Lys	Ile	Thr	Val		Glu	Leu	Lys	Leu	Lys	Ser	Asp	Glu	Asp	Glu	Glu
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			580												

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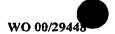
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Asp	Ser	Gly	Leu	Arg	Asp	His	Ser	Val	Arg	Val	Leu	Ile	Ser	Asn	His
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Val	Thr	Pro	Phe	Asp	His	Asn	Ile	Val	Asn	Leu	Leu	Thr		Суз	Ser
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Thr	Pro	Leu	Leu	Asn	Ser	Pro	Pro	Ser	Phe	Val	Cys		Ser	Arg	Gly
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Phe	Met	Glu	Met	Asn	Gly		Gly	Glu	Leu	Val		Ser	Leu	Lys	Arg
	130					135					140	_	_		_
	Cys	Ala	Ser	Thr		Leu	Pro	Pro	Thr		Leu	Leu	Leu	Phe	
145			_	_	150					155	_		1		160
Glu	Glu	Glu	Ala		Asn	Gly	Arg	Glu		Leu	Leu	Arg	Pne		Ser
	_		÷	165		_			170		<b>-</b>	mh	T	175	1101
Trp	Pro	Pne		He	GIN	Asp	vaı		GIN	Pro	Leu	THE	190	GTII	vai
<b>0</b> 7.	•	D	180	**-1	0	**-3	erila an	185	C	2	210	507		ບລາ	Sar
GIN	Arg	195	Leu	Vai	ser	val	200	var	SeI	Asp	WTG	205	ттр	Val	Ser
<b>~</b> 1	Leu		<i>(</i> 1)	C	T 011	Dho		Dro	Dho	ωρ≂	Wal		Gln	Val	Ara
GIU		Leu	тъ	Ser	ьеu	215	vai	PIO	File	7117	220	-7-	GIII	Vul	411.9
m	210 Leu	Ara.	Dro	₹7 <b>⇒</b> ]	ย่อ		G] n	T.e.ii	Cl v	Glu		Δen	Glu	Glu	Phe
225	Den	мy	PLO	Val	230	мg	GIII	Leu	GLY	235	, , , ,	11011	014	024	240
	Leu	720	t/all	Gln.		T.e.ii	ນອງ	Δla	Tare		Len	Glv	Gln	Thr	
ALG	Leu	мg	Val	245	GIII	Tierr	var	niu	250	OLU		O-J		255	1
ጥኮ፦	Arg	ום.ז	ሞኮጕ		Ala	Agn	Lve	Ala		His	Met	Lvs	Ara		Ara
***	ALY	<u> </u>	260	110	- MAC	بإسد	-10	265					270		9
ui e	Pro	Ara		Ara	Pro	Gln	Ser		G) n	Ser	Ser	Phe		Pro	Ser
	ELU		ندا تنابيد												



		275					280					285			
Pro	Gly	Pro	Ser	Pro	Asp	Val	Gln	Leu	Ala	Thr	Leu	Ala	Gln	Arg	Val
	290					295					300				
Lys	Glu	Val	Leu	Pro	His	Val	Pro	Leu	Gly	Val	Ile	Gln	Arg	Asp	Leu
305					310					315					320
Ala	Lys	Thr	Gly	Cys	Val	Asp	Leu	Thr	Ile	Thr	Asn	Leu	Leu	Glu	Gly
				325					330					335	
Ala	Val	Ala	Phe	Met	Pro	Glu	Asp	Ile	Thr	Lys	Gly	Thr	Gln	Ser	Leu
			340					345					350		
Pro	Thr	Ala	Ser	Ala	Ser	Lys	Phe	Pro	Ser	Ser	Gly	Pro	Val	Thr	Pro
		355					360					365			
Gln	Pro	Thr	Ala	Leu	Thr	Phe	Ala	Lys	Ser	Ser	Trp	Ala	Arg	Gln	Glu
	370					375					380				
Ser	Leu	Gln	Glu	Arg	Lys	Gln	Ala	Leu	Tyr	Glu	Tyr	Ala	Arg	Arg	Arg
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 Gly
 Gly
 Val
 Arg
 Ser
 Leu
 Val
 Pro
 Gly
 Pro

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 Leu
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 Leu
 Cys
 Gly
 Leu
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 Glu
 Ala
 Ser
 Gly
 Gly
 Arg

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 Leu
 Val
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 Ser
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 Ile
 Pro
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 Arg
 Val
 Asn
 Trp
 Pro

 Ala
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 Pro
 Gly
 Asp
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 Pro
 Pro
 Arg
 Val
 Asn
 Trp
 Pro

 Gly
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 Glu
 Pro
 Ser
 Leu
 Pro
 Thr
 Thr
 Gly
 Val
 Leu
 Try
 Lys
 Glu
 Asp
 Lys
 Glu
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 Try
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 Glu
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 Asp
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Gly	Pro	Asn	Pro	Arg	Glu	Leu	Leu	Glu	Pro	Leu	Phe	Lys	Gln	Ser	Ser
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Cys	Ser	Tyr	Arg	Ile	Glu	Ser	Tyr	Trp	Thr	Tyr	Glu	Val	Суз	His	Gly
		115					120					125			
Lys	His	Ile	Arg	Gln	Tyr	His	Glu	Glu	Lys	Glu	Thr	Gly	Gln	Lys	Ile
	130					135					140				
Asn	Ile	His	Glu	Tyr	Tyr	Leu	Gly	Asn	Met	Leu	Ala	Lys	Asn	Leu	Leu
145					150					155					160
Phe	Glu	Lys	Glu	Arg	Glu	Ala	Glu	Glu	Lys	Glu	Lys	Ser	Asn	Glu	Ile
				165					170					175	
Pro	Thr	Lys	Asn	Ile	Glu	Gly	Gln	Met	Thr	Pro	Tyr	Tyr	Pro	Val	Gly
			180					185					190		
Met	Gly	Asn	Gly	Thr	Pro	Cys	Ser	Leu	Lys	Gln	Asn	Arg	Pro	Arg	Ser
		195					200					205			
Ser	Thr	Val	Met	Tyr	Ile	Cys	His	Pro	Glu	Ser	Lys	His	Glu	Ile	Leu
	210					215					220				
Ser	Val	Ala	Glu	Val	Thr	Thr	Cys	Glu	Tyr	Glu	Val	Val	Ile	Leu	Thr
225					230					235					240
Pro	Leu	Leu	Суз	Ser	His	Pro	Lys	Tyr	Arg	Phe	Arg	Ala	Ser	Pro	Val
				245					250					255	
Asn	Asp	Ile	Phe	Cys	Gln	Ser	Leu	Pro	Gly	Ser	Pro	Phe	Lys	Pro	Leu
			260					265					270		
Thr	Leu	Arg	Gln	Leu	Glu	Gln	Gln	Glu	Glu	Ile	Leu	Arg	Val	Pro	Phe
		275					280					285			
Arg	Arg	Asn	Lys	Glu	Glu	Asp	Leu	Gln	Ser	Thr	Lys	Glu	Glu	Arg	Phe
	290					295					300				
Pro	Ala	Ile	His	Lys	Ser	Ile	Ala	Ile	Gly	Ser	Gln	Pro	Val	Leu	Thr
305					310					315					320
Val	Gly	Thr	Thr	His	Ile	Ser	Lys	Leu	Thr	Asp	Asp	Gln	Leu	Ile	Lys
				325					330					335	
Glu	Phe	Leu	Ser	Gly	Ser	Tyr	Cys	Phe	Arg	Gly	Gly	Val	Gly	Trp	Trp
			340					345					350		
Lys	Tyr	Glu	Phe	Суз	Tyr	Gly	Lys	His	Val	His	Gln	Tyr	His	Glu	Asp
		355					360					365			
Lvs	Asp	Ser	Glv	Lvs	Thr	Ser	Val	Val	Val	Gly	Thr	Trp	Asn	Gln	Glu

	370	)				375	;				380	)				
Gli	ı His	: Ile	e Glu	ı TrŢ	Ala	Lys	Lys	a Asr	Thi	: Ala	Arg	Ala	а Туз	r His	s Leu	
385	<b>i</b>				390					395	;				400	
Glr	a Asp	Asp	Gly	Thr	Gln	Thr	· Va]	Arg	Met	: Val	Ser	His	; Phe	э Туг	Gly	
				405	;	•			410	)				415	5	
Asr	Gly	' Asp	Ile	e Cys	Asp	Ile	Thi	Asp	Lys	Pro	Arg	Glr	ı Val	Thr	val	
			420	)				425	•				430	)		
Lys	Leu	Lys	Сув	Lys	Glu	Ser	Asp	Ser	Pro	His	Ala	Val	. Thr	: Val	. Tyr	
		435					440					445				
Met			Pro	His	Ser			TYI	Ile	Leu	Gly	Val	Glu	Ser	Pro	
	450					455					460					
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Leu	Pro	Asn														
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Gln	Leu	Arg	Asn	Val	Ala	Leu	Leu	Ala	Leu	Pro	Arg	Val	Leu	Leu	Pro	
			20					25					30			
Leu	His	Phe	Leu	Leu	Pro	Ile	Phe	Leu	Ala	Ala	Val	Pro	Ala	His	Arg	
		35					40					45				
Суз	Ala	Leu	Pro	Gly	Ala	Pro	Ala	Asn	Phe	Ser	His	Gln	Asp	Val	Trp	
	50					55					60					
	Glu	Ala	His	Leu	Pro .	Arg	Glu	Pro	qzA	Gly	Thr	Leu	Ser	Ser	Cys	
65					70					75					80	
Leu	Arg	Phe	Ala		Pro	Gln	Ala	Leu		Asn	Thr	Thr	Leu	-	Glu	
	_		_	85		<b>-</b> -			90					95		
Glu	Arg	Gln	Ser	Arq	Gly (	Glu	Leu	Glu	Asp	Glu	Pro	Ala	Thr	Val	Pro	

105

110

100

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		115					120					125			
Ala	Thr	Glu	Ser	Gln	Val	Gly	Ile	Tyr	Ile	Ile	His	Leu	Glu	Val	Glu
	130					135					140				
Cys	Arg	Trp	Arg	Gln	Ser	Pro	Trp	Glu	Ala	Ala	Gly	Arg	Gly	Leu	Pro
145					150					155					160
Trp	Glu	Glu	Ala	Glu	Ala	Ala	Gly	Leu	Gly	Arg	Asp	Lys	Val	Ser	Tyr
				165					170					175	
Ser	Pro	Ser	Trp	Arg	Glu	Ser	Leu	Gly	Gly	Leu	Leu	Ser	Gly	Met	Glu
			180					185					190		
Trp	Asp	Leu	Val	Суз	Glu	Gln	Lys	Gly	Leu	Asn	Arg	Ala	Ala	Ser	Thr
		195					200					205			
Phe	Phe	Phe	Ala	Gly	Val	Leu	Val	Gly	Ala	Val	Ala	Phe	<sub>.</sub> Gly	Tyr	Leu
	210					215					220				
Ser	Asp	Arg	Phe	Gly	Arg	Arg	Arg	Leu	Leu	Leu	Val	Ala	Tyr	Val	Ser
225					230					235					240
Thr	Leu	Val	Leu	Gly	Leu	Ala	Ser	Ala	Ala	Ser	Val	Ser	Tyr	Val	Met
				245					250					255	
Phe	Ala	Ile	Thr	Arg	Thr	Leu	Thr	Gly	Ser	Ala	Leu	Ala	Gly	Phe	Thr
			260					265					270		
Ile	Ile	Val	Met	Pro	Leu	Glu	Leu	Glu	Trp	Leu	Asp	Val	Glu	His	Arg
		275					280					285			
Thr	Val	Ala	Gly	Val	Leu	Ser	Ser	Thr	Phe	Trp	Thr	Gly	Gly	Val	Met
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Leu	Leu	Ala	Leu	Val	Gly	Tyr	Leu	Ile	Arg	Asp	Trp	Arg	Trp	Leu	Leu
305					310					315					320
Leu	Ala	Val	Thr	Leu	Pro	Cys	Ala	Pro	Gly	Ile	Leu	Ser	Leu	Trp	Trp
				325					330					335	
Val	Pro	Glu	Ser	Ala	Arg	Trp	Leu	Leu	Thr	Gln	Gly	His	Val	Lys	Glu
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Ala	His	Arg	Tyr	Leu	Leu	His	Cys	Ala	Arg	Leu	Asn	Gly	Arg	Pro	Val
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Cys	Glu	Asp	Ser	Phe	Ser	Gln	Glu	Ala	Val	Ser	Lys	Val	Ala	Ala	Gly
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385					390					395	i				400
Arg	Leu	Arg	His	Ile	Ser	Leu	Суз	Cys	Val	Val	Val	Trp	Phe	Gly	Val
				405					410					415	
Asn	Phe	Ser	Tyr	Tyr	Gly	Leu	Ser	Leu	Asp	Val	Ser	Gly	Leu	Gly	Leu
			420					425					430		
Asn	Val	Tyr	Gln	Thr	Gln	Leu	Leu	Phe	Gly	Ala	Val	Glu	Leu	Pro	Ser
		435					440					445			
Lys	Leu	Leu	Val	Tyr	Leu	Ser	Val	Arg	Tyr	Ala	Gly	Arg	Arg	Leu	Thr
	450					455					460				
Gln	Ala	Gly	Thr	Leu	Leu	Gly	Thr	Ala	Leu	Ala	Phe	Gly	Thr	Arg	Leu
465´					470					475					480
Leu	Val	Ser	Ser	Asp	Met	Lys	Ser	Trp	Ser	Thr	Val	Leu	Ala	Val	Met
				485					490					495	
Gly	Lys	Ala	Phe	Ser	Glu	Ala	Ala	Phe	Thr	Thr	Ala	Tyr	Leu	Phe	Thr
			500					505					510		
Ser	Glu		Tyr	Pro	Thr	Val	Leu	Arg	Gln	Thr	Gly	Met	Gly	Leu	Thr
		515					520					525			
		Val	Gly	Arg	Leu	Gly	Gly	Ser	Leu	Ala	Pro	Leu	Ala	Ala	Leu
	530					535					540				
Leu	Asp	Gly	Val	Trp	Leu	Ser	Leu	Pro	Lys	Leu	Thr	Tyr	Gly	Gly	Ile
545					550					555					560
Ala	Leu	Leu	Ala		Gly	Thr	Ala	Leu	Leu	Leu	Pro	Glu	Thr	Arg	Gln
				565					570					575	
Ala	Gln	Leu	Pro	Glu	Thr	Ile	Gln	Asp	Val	Glu	Arg	Lys	Ser	Ala	Pro
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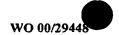
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Суз	Gly	Arg	Arg	Val	Ile	Thr	Ser	Arg	Ile	Val	Gly	Gly	Glu	qaA	Ala
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Glu	Leu	Gly	Arg	Trp	Pro	Trp	Gln	Gly	Ser	Leu	Arg	Leu	Trp	Asp	Sei
	50					55					60				
His	Val	Cys	Gly	Val	Ser	Leu	Leu	Ser	His	Arg	Trp	Ala	Leu	Thr	Ala
65					70					75					80
Ala	His	Cys	Phe	Glu	Thr	Tyr	Ser	Asp	Leu	Ser	Asp	Pro	Ser	Gly	TI
				85					90					95	
Met	Val	Gln	Phe	Gly	Gln	Leu	Thr	Ser	Met	Pro	Ser	Phe	Trp	Ser	Let
			100					105					110		
Gln	Ala	Tyr	Tyr	Thr	Arg	Tyr	Phe	Val	Ser	Asn	Ile	Tyr	Leu	Ser	Pro
		115					120					125			
Arg	Tyr	Leu	Gly	Asn	Ser	Pro	Tyr	Asp	Ile	Ala	Leu	Val	Lys	Leu	Ser
	130					135					140				
Ala	Pro	Val	Thr	Tyr	Thr	Lys	His	Ile	Gln	Pro	Ile	Cys	Leu	Gln	Ala
145					150					155					160
Ser	Thr	Phe	Glu	Phe	Glu	Asn	Arg	Thr	Asp	Cys	Trp	Val	Thr	Gly	TIE
				165					170					175	
Gly	Tyr	Ile	Lys	Glu	Asp	Glu	Ala	Leu	Pro	Ser	Pro	His	Thr	Leu	Glr
			180					185					190		
Glu	Val	Gln	Val	Ala	Ile	Ile	Asn	Asn	Ser	Met	Cys	Asn	His	Leu	Phe
		195					200					205			
Leu	Lys	Tyr	Ser	Phe	Arg	Lys	Asp	Ile	Phe	Gly	Asp	Met	Val	Суз	Alé
	210					215					220				
Gly	Asn	Ala	Gln	Gly	Gly	Lys	Asp	Ala	CAa	Phe	Gly	qeA	Ser	Gly	Gl
225					230					235					240
Pro	Leu	Ala	Суз	Asn	Lys	Asn	Gly	Leu	Trp	Tyr	Gln	Ile	Gly	Val	Va]
				245					250					255	
Ser	Trp	Gly	Val	Gly	Cys	Gly	Arg	Pro	Asn	Arg	Pro	Gly	Val	Tyr	Thr
			260					265					270		
Asn	Ile	Ser	His	His	Phe	Glu	Trp	Ile	Gln	Lys	Leu	Met	Ala	Gln	Sex
		275					280					285			
Gly	Met	Ser	Gln	Pro	Asp	Pro	Ser	Trp	Pro	Leu	Leu	Phe	Phe	Pro	Let

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Cys	Ala	Ser	Pne	Met	ser	rne	GTĀ	vaı	гЛз	Arg	Arg	Trp	Fue	ATa	re
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Gly	Ala	Ala	Leu	Gln	Leu	Ala	Ile	Ser	Thr	Tyr	Ala	Ala	Tyr	Ile	Gly
				85					90					95	
Gly	Tyr	Val	His	Tyr	Gly	Asp	Trp	Leu	Lys	Val	Arg	Met	Tyr	Ser	Arg
			100					105					110		
Thr	Val	Ala	Ile	Ile	Gly	Gly	Leu	Ser	Cys	Val	Gly	Gln	Arg	Cys	Tr
		115					120					125			
Gly	Ala	Val	Pro	Pro	Glu	Thr	Ser	Gln	Pro	Leu	Pro	Ala	Val	His	Arg
	130					135					140				
Pro	Gly	Val	Pro	Gly	Tyr	Leu	Pro	His	Leu	Cys	Gly	Leu	Leu	Thr	Ala
145					150					155					160
Ala	Gln	Gln	Gly	Gly	Pro	Ala	Gly	Val	Ser	Glu	Pro	Ser	Pro	Arg	Arg
				165					170					175	
Gly	Ala	Asp	Asp	Pro	Ala	Val	Leu	Arg	Ala	Val	Trp	His	Pro	Gly	Pro
			180					185					190		
Gly	Leu	Ser	Val	Arg	Leu	Leu	Arg	Asp	Pro	Arg	Суз	Pro	qaA	Pro	Gly
		195					200					205			
Cys	Thr	Ala	Ala	Pro	Cys	His	Ala	Ala	His						
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1				5					10					15	
Ser	Arg	Ile	Asp	Gln	Asp	Asn	Ser	Ser	Phe	Asp	Ser	Leu	Ser	Pro	Glu
			20					25					30		
Pro	Lys	Ser	Arg	Phe	Ala	Met	Leu	Asp	Asp	Val	Lys	Ile	Leu	Ala	Asn
		35			•		40					45			
Gly	Leu	Leu	Gln	Leu	Gly	His	Gly	Leu	Lys	Asp	Phe	Val	His	Lys	Thr
	50					55					60				
T	<b>~1</b>	C1 5	T10	A on	A	T10	Dhe	Gln	T 170	T.011	λen	Tle	Phe	Acn	Gln



65					70					75	•				80
Ser	Phe	Tyr	Asp	Leu	Ser	Leu	Gln	Thr	Ser	Glu	ılle	Lys	Glu	Glu	Glu
				85					90	)				95	<b>i</b>
Lys	Glu	Leu	Arg	Arg	Thr	Thr	Tyr	Lys	Leu	Gln	Val	. Lys	. Asn	Glu	Glu
			100					105	,				110	ı	
Val	Lys	Asn	Met	Ser	Leu	Glu	Leu	Asn	Ser	. Ta	Leu	Glu	Ser	Leu	Let
		115					120					125	ı		
Glu	Glu	Lys	Ile	Leu	Leu	Gln	Gln	Lys	Val	Lys	Туг	Leu	Glu	Glu	Glr
	130					135					140				
Leu	Thr	Asn	Leu	Ile	Gln	Asn	Gln	Pro	Glu	Thr	Pro	Glu	His	Pro	Glu
145					150					155					160
Val	Thr	Ser	Leu	Lys	Thr	Phe	Val	Glu	Lys	Gln	Asp	Asn	Ser	Ile	Lys
				165					170					175	
qeA	Leu	Leu	Gln	Thr	Val	Glu	Asp	Gln	Tyr	Lys	Gln	Leu	Asn	Gln	Gln
			180					185					190		
His	Ser	Gln	Ile	Lys	Glu	Ile	Glu	Asn	Gln	Leu	Arg	Arg	Thr	Ser	Ile
		195					200					205			
Gln	Glu	Pro	Thr	Glu	Ile	Ser	Leu	Ser	Ser	Lys	Pro	Arg	Ala	Pro	Arg
	210					215					220				
Thr	Thr	Pro	Phe	Leu	Gln	Leu	Asn	Glu	Ile	Arg	Asn	Val	Lys	His	Asp
225					230					235					240
Gly	Ile	Pro	Ala	Glu	Cys	Thr	Thr	Ile	Tyr	Asn	Arg	Gly	Glu	His	Thr
				245					250			-		255	
Ser	Gly	Met	Tyr	Ala	Ile	Arg	Pro	Ser	Asn	Ser	Gln	Val	Phe	His	Val
			260					265					270		
Tyr	Cys	Asp	Val	Ile	Ser	Gly	Ser	Pro	Trp	Thr	Leu	Ile	Gln	His	Arg
		275					280					285			
Ile	Asp	Gly	Ser	Gln	Asn	Phe	Asn	Glu	Thr	Trp	Glu	Asn	Tyr	Lys	Tyr
	290					295					300				
Gly	Phe	Gly	Arg	Leu	Asp	Gly	Glu	Phe	Trp	Leu	Gly	Leu	Glu	Lys	Ile
305					310					315					320
Tyr	Ser	Ile	Val	Lys	Gln	Ser	Asn	Tyr	Val	Leu	Arg	Ile	Glu	Leu	Glu
				325					330					335	
Asp	Trp	Lys		Asn	Lys	His	Tyr	Ile	Glu	Tyr	Ser	Phe	Tyr	Leu	Gly
			240					245					250		

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Asn His Glu Thr Asn Tyr Thr Leu His Leu Val Ala Ile Thr Gly Asn 355 360 365 Val Pro Asn Ala Ile Pro Glu Asn Lys Asp Leu Val Phe Ser Thr Trp 375 Asp His Lys Ala Lys Gly His Phe Asn Cys Pro Glu Gly Tyr Ser Gly 390 395 400 385 Gly Trp Trp Trp His Asp Glu Cys Gly Glu Asn Asn Leu Asn Gly Lys 405 410 Tyr Asn Lys Pro Arg Ala Lys Ser Lys Pro Glu Arg Arg Arg Gly Leu 425 Ser Trp Lys Ser Gln Asn Gly Arg Leu Tyr Ser Ile Lys Ser Thr Lys 445 435 440 Met Leu Ile His Pro Thr Asp Ser Glu Ser Phe Glu 460 450 455

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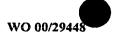
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Val Gly Leu Glu Ser Gln Cys Arg Pro Gln Glu Leu Asp Gln Pro Pro
100 105 110

Pro Tyr Ser Thr Val Val Ile Pro Pro Ala Pro Glu Glu Glu Gln Pro



115 120 125 Ser His Pro Glu Gly Ser Arg Arg Ala Lys Leu Glu Gln Arg Arg Met 135 Ala Ser Glu Gly Ser Met Ala Gln Glu Gly Ser Pro Gly Arg Ala Pro 145 150 155 Ile Asn Leu Arg Leu Arg Gly Pro Arg Ala Val Ser Thr Ala Pro Asp 165 170 175 Leu Gln Ser Leu Ala Ala Val Pro Thr Leu Glu Pro Leu Thr Pro Pro 185 Pro Ala Tyr Asp Val Cys Phe Gly His Pro Asp Asp Asp Ser Val Phe 195 200 205 Tyr Glu Asp Asn Trp Ala Pro Pro 210 215 <210> 41

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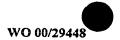
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TTE	ту	C GI	n re	u Ar	g va.	I Thi	r GL	y Arg	Th	r Gli	n Ası	o Glu	ıIl	e Le	u Phe	•
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Ser	Asr	se:	r Th	r Ar	j Lei	ı Sei	: Phe	e Glu	Thi	Lys	a Arç	, Ile	e Se	r Va	l Phe	•
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Ile	Glr	Thi	r Ası	p Lys	Ala	a Let	туг	Lys	Pro	Lys	Glr.	Glu	ı Va	l Ly	s Phe	•
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									_						tta	
Arg	Ile	· Val	l Thi	Let	Phe	e Ser	Asp	Phe	Lys	Pro	Tyr	Lys	Thi	Se	Leu	
	150	)				155					160	)				
										_				-	g ttg	
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Gln Thr Ser Glu Gly I	lle Pro Ile Met Arg	Trp Leu Ser Arg Gln Arg	
1160	1165	1170	
aat age ttg ggt ggt t	tt gea tet act cag	gat acc act gtg gct tta	3608
Asn Ser Leu Gly Gly P	he Ala Ser Thr Gln	Asp Thr Thr Val Ala Leu	
1175	1180	1185	
aag get etg tet gaa t	tt gca gcc cta atg	aat aca gaa agg aca aat	3656
Lys Ala Leu Ser Glu P	he Ala Ala Leu Met	Asn Thr Glu Arg Thr Asn	
1190	1195	1200	
atc caa gtg acc gtg a	acg ggg cct agc tca	cca agt cct gta aag ttt	3704
Ile Gln Val Thr Val T	thr Gly Pro Ser Ser	Pro Ser Pro Val Lys Phe	
1205	1210	1215 1220	
ctg att gac aca cac a	ac ege tta etc ett	cag aca gca gag ctt gct	3752

Leu	TTE	e Asi	o Thr	HIS	a Ast	Arg	Let	Let	Let	ı Glr	1 Thi	: Alt	a GI	u Lei	ı Ala	
				122	25				123	10				12:	35	
gtg	gta	cag	g cca	acq	g gca	gtt	aat	att	tcc	gca	a aat	ggt	: tti	t gga	ttt	3800
Val	Val	Glr	Pro	Th	: Ala	Val	Asr	lle	Ser	Ala	a Asr	Gly	Phe	e Gly	Phe	
			124	0				124	5				125	50		
gct	att	: tgt	cag	cto	aat	gtt	gta	tat	aat	gtg	aag	gct	tet	ggg	tet	3848
Ala	Ile	Cys	Gln	Let	. Asn	Val	Val	Tyr	Asn	Val	. Lys	Ala	Sei	Gly	Ser	
		125	5				126	0				126	5			
tct	aga	aga	cga	aga	tct	atc	caa	aat	caa	gaa	gcc	ttt	gat	tta	gat	3896
Ser	Arg	Arg	Arg	Arg	Ser	Ile	Gln	Asn	Gln	Glu	Ala	Phe	Asp	Leu	Asp	
	127	0				127	5				128	0				
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Val	Ala	Val	Lys	Glu	Asn	Lys	Asp	Asp	Leu	Asn	His	Val	Asp	Leu	Asn	
128	5				129	0				129	5				1300	
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Val	Суз	Thr	Ser	Phe	Ser	Gly	Pro	Gly	Arg	Ser	Gly	Met	Ala	Leu	Met	
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Glu	Val	Asn	Leu	Leu	Ser	Gly	Phe	Met	Val	Pro	Ser	Glu	Ala	Ile	Ser	
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Leu	Ser	Glu	Thr	Val	Lys	Lys	Val	Glu	Tyr	Asp	His	Gly	Lys	Leu	Asn	
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Leu	Tyr	Leu	qzA	Ser	Val	Asn	Glu	Thr	Gln	Phe	Суз	Val	Asn	Ile	Pro	
	1350	)				1355	<b>j</b>				1360	)				
gct	gtg	aga	aac	ttt	aaa	gtt	tca	aat	acc	caa	gat	gct	tca	gtg	tcc	4184
Ala	Val	Arg	Asn	Phe	Lys	Val	Ser	Asn	Thr	Gln	Asp	Ala	Ser	Val	Ser	
1365					1370	)				1375	5				1380	
ata	gtg	gat	tac	tat	gag	cca	agg	aga	cag	gcg	gtg	aga	agt	tac	aac	4232
Ile	Val	Asp	Tyr	Tyr	Glu	Pro	Arg	Arg	Gln	Ala	Val	Arg	Ser	Tyr	Asn	
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tct	gaa	gtg	aag	ctg	tcc	tcc	tgt	gac	ctt	tge	agt	gat	gtc	cag	ggc	4280
Ser	Glu	Val	Lys	Leu	Ser	Ser	Cys	Asp	Leu	Суз	Ser	Asp	Val	Gln	Gly	
			1400					1405					1410	)		

tge egt eet tgt gag gat gga get te	a ggc tcc cat cat cac tct tca 432
Cys Arg Pro Cys Glu Asp Gly Ala Se	r Gly Ser His His His Ser Ser
1415 1420	1425
gto att ttt att tto tgt tto aag ot	t ctg tac ttt atg gaa ctt tgg 437
val Ile Phe Ile Phe Cys Phe Lys Le	ı Leu Tyr Phe Met Glu Leu Trp
1430 1435	1440
ctg tgatttattt ttaaaggact ctgtgtaa	ca ctaacatttc cagtagtcac a 443
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Met Phe Pro	o Ala Gly Pro Pro Ser His Ser
1	5 10
ete ete egg ete ece etg etg eag tt	g ctg cta ctg gtg gtg cag gcc 15
Leu Leu Arg Leu Pro Leu Leu Gln Le	ı Leu Leu Leu Val Val Gln Ala
15	20 25
gtg ggg agg ggg ctg ggc cgc gcc ag	c ceg gee ggg gge cee etg gaa 20
Val Gly Arg Gly Leu Gly Arg Ala Se	r Pro Ala Gly Gly Pro Leu Glu
30 3!	5 40
gat gtg gtc atc gag agg tac cac atc	c ecc agg gec tgt ecc egg gaa 25
Asp Val Val Ile Glu Arg Tyr His Ile	Pro Arg Ala Cys Pro Arg Glu
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Val Gln Met Gly Asp Phe Val Arg Tyr	His Tyr Asn Gly Thr Phe Glu
60 65	70

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Asp	Gly	Ly:	3 Lys	3 Phe	a As	Sei	c Sei	туз	c Asp	Ar	g Asi	n Th	r Le	u Va	l Ala	<b>.</b>
75	<b>;</b>				8	0				8:	5				90	
ato	gto	gto	g ggt	t gtg	<b>3 9 9</b>	gege	cto	ato	act	gg:	ate	g gad	e eg	a gg	e ctc	399
Ile	Val	. Val	l Gly	y Val	L Gly	Arg	J Let	ı Ile	Thr	Gly	/ Met	t Ası	o Ar	g Gl	y Leu	
				95	5				100	)				10	5	
atg	ggo	ato	, tgt	gto	aac	gaç	gegg	cga	cgo	cto	att	t gt	g cci	t acc	c cac	447
Met	Gly	Met	Cys	Va]	Ası	ı Glu	Arg	Arg	Arg	Lev	ı Ile	e Val	l Pro	o Pro	His	•
			110	)				115	<b>i</b>				120	כ		
ctg	ggc	tat	ggg	ago	ato	ggo	ctg	gcg	999	cto	att	CCE	a cc	g gat	gee	495
Leu	Gly	Туг	Gly	Ser	: Ile	Gly	Leu	Ala	Gly	Leu	Ile	Pro	Pro	Asp	Ala	
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acc	ctc	tac	tto	gat	gtg	gtt	ctg	ctg	gat	gtg	tgg	, aac	aag	g gaa	a gac	543
Thr	Leu	Tyr	Phe	Asp	Val	Val	Leu	Leu	Asp	Val	Tre	) Asn	Lys	Glu	qaA ı	
	140					145					150	)				
acc	gtg	cag	gtg	age	aca	ttg	ctg	ege	ccg	ccc	cac	tgo	ccc	egg	atg	591
Thr	Val	Gln	Val	Ser	Thr	Leu	Leu	Arg	Pro	Pro	His	Суз	Pro	Arg	Met	
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qaA	Gly	Thr	Ser	Phe	Asp	Thr	Ser	Tyr	Ser	Lys	Gly	Gly	Thr	Tyr	Asp	
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Thr	Tyr	Val	Gly	Ser	Gly	Trp	Leu	Ile	Lys	Gly	Met	Asp	Gln	Gly	Leu	
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Leu	Gly	Met	Cys	Pro	Gly	Glu	Arg	Arg	Lys	Ile	Ile	Ile	Pro	Pro	Phe	
	220					225					230					
etg	gcc	tat	ggc	gag	aaa	ggc	tat	<b>9</b> 99	acg	gtg	atc	ccc	cca	cag	gee	831
eu	Ala	Tyr	Gly	Glu	Lys	Gly	Tyr	Gly	Thr	Val	Ile	Pro	Pro	Gln	Ala	
235					240					245					250	
						ctc							_	_	_	879
er .	Leu	Val	Phe	Hìs	Val	Leu	Leu	Ile	qzA	Val	His	Asn	Pro	Lys	Asp	

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Ala Val Gln Leu	Glu Thr Leu Glu	Leu Pro Pro Gl	y Cys Val Arg <i>P</i>	<b>l</b> rg
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gee ggg gee ggg	gac ttc atg cgc	tac cac tac aa	t ggc tcc ttg a	atg 975
Ala Gly Ala Gly	Asp Phe Met Arg	Tyr His Tyr As	n Gly Ser Leu N	<u>let</u>
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Asp Gly Thr Leu	Phe Asp Ser Ser	Tyr Ser Arg As	n His Thr Tyr A	Asn
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acc tat atc ggg	cag ggt tac ato	atc ccc ggg at	g gac cag ggg c	etg 1071
Thr Tyr Ile Gly	Gln Gly Tyr Ile	: Ile Pro Gly Me	t Asp Gln Gly I	eu
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cag ggt gcc tgc	atg ggg gaa cgc	e cgg aga att ac	e ate ece ecg e	eac 1119
Gln Gly Ala Cys	Met Gly Glu Arg	Arg Arg Ile Th	r Ile Pro Pro E	lis
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Leu Ala Tyr Gly	Glu Asn Gly Thr	Gly Asp Lys Il	e Pro Gly Ser A	la
350		355	360	
gtg cta atc ttc	aac gtc cat gtc	att gac ttc ca	c aac cct gcg g	gat 1215
Val Leu Ile Phe	Asn Val His Val	. Ile Asp Phe Hi	s Asn Pro Ala A	Asp
365	370	1	375	
gtg gtg gaa atc	agg aca ctg tcc	egg cca tct ga	g acc tgc aat g	gag 1263
Val Val Glu Ile	Arg Thr Leu Ser	Arg Pro Ser Gl	u Thr Cys Asn G	lu
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		. cga tac cat ta		
Thr Thr Lys Leu	Gly Asp Phe Val	Arg Tyr His Ty	r Asn Cys Ser I	eu
395	400	405	4	110
		tcg cat gac ta		
Leu Asp Gly Thr	Gln Leu Phe Thr	Ser His Asp Ty		Sln
	415	420	425	
gag gcg act ctc	ggg gcc aac aag	gtg atc gaa gg	c ctg gac acg g	ge 1407
Glu Ala Thr Leu	Gly Ala Asn Lys	Val Ile Glu Gl	y Leu Asp Thr G	Sly
430		435	440	
ctg cag ggc atg	tgt gtg gga gag	agg cgg cag ct	e atc gtg ccc c	ecg 1455



Leu Gln Gly Met Cys Val Gly Glu Arg Arg Gln Leu Ile Val Pro Pro	
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His Leu Ala His Gly Glu Ser Gly Ala Arg Gly Val Pro Gly Ser Ala	
460 465 470	
gtg ctg ctg ttt gag gtg gag ctg gtg tcc cgg gag gat ggg ctg ccc	1551
Val Leu Leu Phe Glu Val Glu Leu Val Ser Arg Glu Asp Gly Leu Pro	
475 480 485 490	
aca gge tac etg ttt gtg tgg cac aag gae eet eet gee aac etg ttt	1599
Thr Gly Tyr Leu Phe Val Trp His Lys Asp Pro Pro Ala Asn Leu Phe	
495 500 505	
gaa gac atg gac ctc aac aag gat ggc gag gtc cct ccg gag gag ttc	1647
Glu Asp Met Asp Leu Asn Lys Asp Gly Glu Val Pro Pro Glu Glu Phe	
510 515 520	
tee ace tte ate aag get caa gtg agt gag gge aaa gga ege ete atg	1695
Ser Thr Phe Ile Lys Ala Gln Val Ser Glu Gly Lys Gly Arg Leu Met	
525 530 535	
eet ggg eag gae eet gag aaa ace ata gga gae atg tte eag aac eag	1743
Pro Gly Gln Asp Pro Glu Lys Thr Ile Gly Asp Met Phe Gln Asn Gln	
540 545 550	
gac ege aac cag gac gge aag ate aca gte gac gag ete aag etg aag	1791
Asp Arg Asn Gln Asp Gly Lys Ile Thr Val Asp Glu Leu Lys Leu Lys	
555 560 565 570	
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Ser Asp Glu Asp Glu Glu Arg Val His Glu Glu Leu	
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acceptette tettecatee etaaaceaet teettaaaat etttegattt geaaageeaa	2080
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Met Glu Leu Pro Ser Gly Pro Gly	
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ceg gag egg ete ttt gae teg eae egg ett eeg ggt gae tge tte eta	160
Pro Glu Arg Leu Phe Asp Ser His Arg Leu Pro Gly Asp Cys Phe Leu	
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Leu Leu Val Leu Leu Tyr Ala Pro Val Gly Phe Cys Leu Leu Val	
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Leu Arg Leu Phe Leu Gly Ile His Val Phe Leu Val Ser Cys Ala Leu	
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Pro Asp Ser Val Leu Arg Arg Phe Val Val Arg Thr Met Cys Ala Val	
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Leu Gly Leu Val Ala Arg Gln Glu Asp Ser Gly Leu Arg Asp His Ser	
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gtc agg gtc ctc att tcc aac cat gtg aca cct ttc gac cac aac ata	400
Val Arg Val Leu Ile Ser Asn His Val Thr Pro Phe Asp His Asn Ile	

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gta	aat	ttg	ctt	acc	acc	tgt	age	acc	cct	. cta	cto	aat	agt		ccc	448
Val	Asn	Leu	Leu	Thr	Thr	Сув	Ser	Thr	Pro	Leu	Let	ı Asn	Ser	Pro	Pro	
105					110	)				115	,				120	
agc	ttt	gtg	tgc	tgg	tct	cgg	ggc	tto	atg	gag	ato	aat	ggg	cgg	999	496
Ser	Phe	Val	Суз	Trp	Ser	Arg	Gly	Phe	Met	Glu	Met	Asn	Gly	Arc	g Gly	
				125					130	)				135	<b>5</b> .	
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Glu	Leu	Val	Glu	Ser	Leu	Lys	Arg	Phe	Cys	Ala	Ser	Thr	Arg	Leu	Pro	
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ccc	act	cct	ctg	ctg	cta	ttc	cct	gag	gaa	gag	gcc	acc	aat	ggo	egg	592
Pro	Thr	Pro	Leu	Leu	Leu	Phe	Pro	Glu	Glu	Glu	Ala	Thr	Asn	Gly	Arg	
		155					160					165				
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Glu	Gly	Leu	Leu	Arg	Phe	Ser	Ser	Trp	Pro	Phe	Ser	Ile	Gln	Asp	Val	
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Val	Gln	Pro	Leu	Thr	Leu	Gln	Val	Gln	Arg	Pro	Leu	Val	Ser	Val	Thr	
185					190	,				195					200	
gtg	tca	gat	gcc	tcc	tgg	gtc	tca	gaa	ctg	ctg	tgg	tca	ctt	ttc	gtc	736
Val	Ser	Asp	Ala	Ser	Trp	Val	Ser	Glu	Leu	Leu	Trp	Ser	Leu	Phe	Val	
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cct	ttc	acg	gtg	tat	caa	gta	agg	tgg	ctt	cgt	cct	gtt	cat	cgc	caa	784
Pro	Phe	Thr	Val	Tyr	Gln	Val	Arg	Trp	Leu	Arg	Pro	Val	His	Arg	Gln	
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cta	ggg	gaa	gcg	aat	gag	gag	ttt	gca	ctc	cgt	gta	caa	cag	ctg	gtg	832
Leu	Gly	Glu	Ala	Asn	Glu	Glu	Phe	Ala	Leu	Arg	Val	Gln	Gln	Leu	Val	
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gcc	aag	gaa	ttg	ggc	cag	aca	ggg	aca	cgg	ctc	act	cca	gct	gac	aaa	880
Ala	Lys	Glu	Leu	Gly	Gln	Thr	Gly	Thr	Arg	Leu	Thr	Pro	Ala	qaA	Lys	
	250					255					260					
gca	gag	cac	atg	aag	cga	caa	aga	cac	ccc	aga	ttg	cgc	ccc	cag	tca	928
Ala	Glu	His	Met	Lys	Arg	Gln	Arg	His	Pro	Arg	Leu	Arg	Pro	Gln	Ser	
265					270					275					280	
gcc	cag	tct	tct	ttc	cct	ccc	tcc	cct	aat	cct	tct	cct	gat	gtg	caa	976

PCT/JP99/06412

### 90/233

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Leu	Ala	Thr	Leu	Ala	Gln	Arg	Val	Lys	Glu	Val	Leu	Pro	His	Val	Pro	
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Leu	Gly	Val	Ile	Gln	Arg	Asp	Leu	Ala	Lys	Thr	Gly	Суз	Val	Asp	Leu	
		315					320					325				
act	atc	act	aat	ctg	ctt	gag	<b>9</b> 99	gcc	gta	gct	ttc	atg	cct	gaa	gac	1120
Thr	Ile	Thr	Asn	Leu	Leu	Glu	Gly	Ala	Val	Ala	Phe	Met	Pro	Glu	Asp	
	330					335					340					
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Ile	Thr	Lys	Gly	Thr	Gln	Ser	Leu	Pro	Thr	Ala	Ser	Ala	Ser	Lys	Phe	
345					350					355					360	
ccc	agc	tct	ggc	ccg	gtg	acc	cct	cag	cca	aca	gcc	cta	aca	ttt	gcc	1216
Pro	Ser	Ser	Gly	Pro	Val	Thr	Pro	Gln	Pro	Thr	Ala	Leu	Thr	Phe	Ala	
				365					370					375		
aag	tct	tcc	tgg	gcc	cgg	cag	gag	agc	ctg	cag	gag	cgc	aag	caa	gca	1264
Lys	Ser	Ser	Trp	Ala	Arg	Gln	Glu	Ser	Leu	Gln	Glu	Arg	ГÀЗ	Gln	Ala	
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cta	tat	gaa	tac	gca	aga	agg	aga	ttc	aca	gag	aga	cga	gcc	cag	gag	1312
Leu	Tyr	Glu	Tyr	Ala	Arg	Arg	Arg	Phe	Thr	Glu	Arg	Arg	Ala	Gln	Glu	
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gct	gac	tgag	gata	aaa g	ggaac	agge	at g	gcaco	cage	a gcc	gcag	gac .	ggag	jacto	aaa aa	1370
Ala	Asp															
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cago	ccto	eac c	caac	tcac	ca ac	aggo	tgga	a tgg	gtg	ggtg	gtas	aaag	ggg e	agge	atgagg	1430
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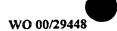
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Ten	ser	rea	335	ııp	AST	Pro	GTU		ATS	Arg	Trp	Leu		Thr	GIn	
aaa	ast.	at-		<b>~</b> 0~	<b>~</b> ~	<b>a</b> n-		340	<b>+</b>			مليم علا	345			1100
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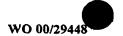
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Gin Giu ala ala Pro Lou Sor Ciu Pro Cue Giu and are Vol. Tie Min	

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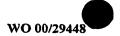
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Gln	Leu	Leu	Gly	Leu	Leu	Pro	Glu	His	Met	Ala	Glu	Lys	Leu	Cys	Glu
		275					280					285			
Ala	Trp	Ala	Phe	Gly	Gln	Ser	His	Gln	Thr	Gly		Val	Ala	Leu	Gly
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Leu	Leu	Thr	Cys	Leu	Leu	Ala	Met	Leu	Leu	Ala	Gly	Arg	Ile	Arg	Leu
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Ar	g Arg	g Ile	e As	p Ala	a Phe	е Суз	3 Thi	Cys	s Le	ı Trj	e Ala	a Lev	ı Lev	Lev	Gly
				32					330					335	
Lev	ı His	Let	ı Ala	a Glu	ı Glr	His	3 Lev	ı Glı	n Ala	a Ala	a Sei	Pro	Ser	Tr	Leu
			340	)				345	5				350	)	
Ası	Thr	Let	ı Lys	Phe	e Ser	Thi	Thr	Sez	Let	Cys	Cys	Leu	Val	Gly	Phe
		355	5				360	)				365			
Thi	: Ala	Ala	a Val	l Ala	Thr	Arg	J Lys	Ala	Thr	Gly	Pro	Arg	Arg	Phe	Arg
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			20					25					30		
Arg	Ser	Leu	Trp	Ser	Ser	Leu	Суз	Leu	Gly	Pro	Ala	Pro	Ala	Pro	Pro
		35					40					45			
Gly	Pro	Val	Ser	Pro	Glu	Gly	Arg	Leu	Ala	Ala	Ala	Trp	Asp	Ala	Leu
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65					70					75					80
Ala	Cys	Val	Asp	Val	Val	Leu	Ser	Gly	Val	Lys	Leu	Leu	Gln	Ala	Leu
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Gly	Leu	Ser	Pro	Gly	Asn	Gly	Lys	Asp	His	Ser	Ile	Leu	His	Ser	Arg
			100					105					110		
Asn	Asp	Leu	Glu	Glu	Ala	Phe	Ile	His	Phe	Met	Trp	Lys	Gly	Ala	Ala
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				165					170					175	
Leu	Cys	Gly	Pro	Val	Gly	Pro	Arg	Leu	His	Glu	Leu	Leu	Asp	Asp	Asn
			180					185					190		
Val	Phe	Val	Pro	Pro	Glu	Ser	Leu	Gln	Glu	Val	Asp	Glu	Phe	His	Leu
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Ile	Leu	Glu	Tyr	Gln	Ala	Gly	Glu	Glu	Trp	Gly	Gln	Leu	Lys	Ala	Pro
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Leu	Gln	Arg	Lys	Arg	Leu	Leu	Glu	Val	Val	Thr	Ser	Ile	Ser	Asp	Ile
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Pro	Thr	Gly	Ile	Pro	Val	His	Leu	Glu	Leu	Ala	Ser	Met	Thr	Asn	Arg
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Glu	Leu	Met	Ser	Ser	Ile	Val	His	Gln	Gln	Val	Phe	Pro	Ala	Val	
305					310					315					320
Ser	Leu	Gly	Leu	Asn	Glu	Gln	Glu	Leu	Leu	Phe	Leu	Thr	Gln		Ala
				325					330					335	
Ser	Gly	Pro	His	Ser	Ser	Leu	Ser	Ser	Trp	Asn	Gly	Val		Asp	Val
			340					345					350		
Gly	Met	Val	Ser	Asp	Ile	Leu	Phe	Trp	Ile	Leu	Lys		His	GLY	Arg
		355					360					365			_
Ser	Lys	Ser	Arg	Ala	Ser		Leu	Thr	Arg	Ile		Phe	His	Thr	Leu
	370					375					380		_		
Val	Tyr	His	Ile	Leu	Ala	Thr	Val	Asp	Gly		Trp	Ala	Asn	GIn	
385					390					395		•		_	400
Ala	Ala	Val	Ala		Gly	Ala	Arg	Val		Gly	Thr	Gin	Ala		ATa
				405					410			_ •		415	<b>0</b> 3
Thr	Glu	Thr		Asp	Thr	Ser	Arg		Ser	Leu	Arg	ALA		GIN	GIU
			420					425					430		

Phe	Met	Th	r Sei	r His	s Sei	c Glu	u Ala	a Gly	y Sei	r Arg	, Ile	va:	l Leu	Asr	) Pr
		439	5				440	)				445	5		
Asn	Lys	Pro	val	l Vai	l Glu	Tr	o His	Arg	g Glu	ı Gly	7 Ile	Se)	Phe	His	Ph
	450	)				455	5				460	)			
Thr	Pro	Va]	Let	ı Val	L Cys	Lys	a Asp	Pro	Ile	e Arg	Thr	Va]	l Gly	Leu	Gl
465					470					475					48
Asp	Ala	Ile	e Ser	Ala	a Glu	Gly	/ Leu	Phe	туг	Ser	Glu	Va]	. His	Pro	Hi
				485	•				490	)				495	
Tyr															
	0> 6														
	1> 4														
	2> P														
	<i>3&gt;</i> н 0> б		sapi	ens											
			ui e	Tou	Dhe	7.20	. Wal	<b>~</b> 1••	· ~1~		<b>~</b> 3	<b>a</b> 1	D	Db.a	D
1	Tierr	Val	nis	Б		ALG	val	GTĀ	10	Arg	GLY	стХ	PIO	15	PIC
	Ara	Leu	Len			T.eu	Ara	Dhe		Thr	Dhe	Sor	Ale		Arc
CLJ	9	204	20		110	DC.	, 111 g	25	GIII		FIIG	Ser	30	Val	M.
Tvr	Ser	azA			Ara	Ser	Ser		Leu	Leu	Ara	Ala		Ala	His
		35	4	-2-	<i>J</i>		40					45	-		
Leu	Arg	Ser	Gln	Leu	Trp	Ala	-	Leu	Pro	Arg	Ala		Leu	Ala	Pro
	50				•	55				5	60				
Arg	Trp	Ser	Pro	Ser	Ala	Trp	Сув	Trp	Val	Gly	Gly	Ala	Leu	Leu	Gly
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Pro	Met	Val	Leu	Ser	Lys	His	Pro	His	Leu	Суз	Leu	Val	Ala	Leu	Cys
				85					90					95	
Glu	Ala	Glu	Glu	Ala	Pro	Pro	Ala	Ser	Ser	Thr	Pro	His	Val	Val	Gly
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Ser	Arg	Phe	Asn	Trp	Lys	Leu	Phe	Trp	Gln	Phe	Leu	His	Pro	His	Leu
		115			•		120					125			
Leu	Val	Leu	Gly	Val	Ala	Val	Val	Leu	Ala	Leu	Gly	Ala	Ala :	Leu	Val
	130					135					140				
Asn	Val	Gln	Ile	Pro	Leu	Leu	Leu	Gly	Gln	Leu	Val	Glu	Val '	Val	Ala
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Lys	Tyr	Thr	Arg	Asp	His	Val	Gly	Ser	Phe	Met	Thr	Glu	Ser	Gln	Ası
	•			165					170					175	
Leu	Ser	Thr	His	Leu	Leu	Ile	Leu	Tyr	Gly	Val	Gln	Gly	Leu	Leu	Thi
			180					185					190		
Phe	Gly	Tyr	Leu	Val	Leu	Leu	Ser	His	Val	Gly	Glu	Arg	Met	Ala	Va]
		195					200					205			
Asp	Met	Arg	Arg	Ala	Leu	Phe	Ser	Ser	Leu	Leu	Arg	Tyr	Cys	Gln	Pro
	210					215					220				
Gln	Gly	Ala	Glu	Leu	Gly	Gln	Asp	Ile	Thr	Phe	Phe	Asp	Ala	Asn	Lys
225					230					235					240
Thr	Gly	Gln	Leu	Val	Ser	Arg	Leu	Thr	Thr	Asp	Val	Gln	Glu	Phe	Lys
				245					250					255	
Ser	Ser	Phe	Lys	Leu	Val	Ile	Ser	Gln	Gly	Leu	Arg	Ser	Cys	Thr	Gln
			260					265					270		
Val	Ala	Gly	Суз	Leu	Val	Ser	Leu	Ser	Met	Leu	Ser	Thr	Arg	Leu	Thr
		275					280					285			
Leu	Leu	Leu	Met	Val	Ala	Thr	Pro	Ala	Leu	Met	Gly	Val	Gly	Thr	Leu
	290					295					300				
Met	Gly	Ser	Gly	Leu	Arg	Lys	Leu	Ser	Cys	Gln	Cys	Gln	Glu	Gln	Ile
305					310					315					320
Ala	Arg	Ala	Met	Gly	Val	Ala	Asp	Glu	Ala	Leu	Gly	Asn	Val	Arg	Thr
				325					330					335	
Val	Arg	Ala	Phe	Ala	Met	Glu	Gln	Arg	Glu	Glu	Glu	Arg	Tyr	Gly	Ala
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Glu	Leu	Glu	Ala	Cys	Arg	Cys	Arg	Ala	Glu	Glu	Leu	Gly	Arg	Gly	Ile
		355					360					365			
Ala	Leu	Phe	Gln	Gly	Leu	Ser	Asn	Ile	Ala	Phe	Asn	Cys	Met	Val	Leu
	370					375					380				
Gly	Thr	Leu	Phe	Ile	Gly	Gly	Ser	Leu	Val	Ala	Gly	Gln	Gln	Leu	Thr
385					390					395					400
Gly	Gly	Asp	Leu	Met	Ser	Phe	Leu	Val	Ala	Ser	Gln	Thr	Val	Gln	Arg
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Leu															

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			20	I				25					30		
Ser	Ser	Val	Leu	Pro	Pro	Phe	Trp	Ala	Lys	Leu	Val	Val	Gly	Ser	Val
		35					40					45			
Ala			Суз	Phe	Ala	_	Ser	Tyr	Asp	Gly	-	Phe	Val	Phe	Asp
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_	Ser	Glu	Ala	Ile		Asn	Asn	Lys	Val		Gly	Val	Val	Gly	_
<b>65</b>					70					75					80
Ala	Asp	Leu	Leu	Cys	Ala	Leu	Phe	Phe		Leu	Ser	Phe	Leu	_	Tyr
_	_			85		_	_	_	90	_=			_	95	
Cys	Lys	Ala		Arg	GLu	Ser	Asn		Glu	GIĀ	Ala	His		Ser	Thr
<b>5</b> 5-	<b></b>	**-1	100	~	0	<b>-1</b> -	<b>51</b> -	105	<b>~1</b> ~~	••-	**-1	22-	110	•	<b>2</b>
Pne	TIP		Leu	Leu	ser	TTE		Leu	GTĀ	ALA	var		Met	Leu	Cys
T 470	CI.	115	<i>0</i> 1 <i>11</i>	Ile	mb~	1701	120	C1.,	Tou	7 an	7 J m	125	Pho	Nan	Tle
тув	130		GTÅ	TTG	TILL	135	Leu	GŢĀ	TIERT	ASII	140	Val	File	wab	TTE
וום.			Glv	Lys	Pho		t/a1	T.esu	Glu	בוד		Gln	Tage	Wal	Len
145	vul	***	GLY	פעם	150	no	·	Leu	GLU	155	var	GLII	туз	VUI	160
	Lvs	Asp	Lvs	Ser		Glu	Asn	Leu	Glv	-	Leu	Ara	Asn	Glv	
		F	-1-	165					170			5		175	~ <b>_</b>
Leu	Leu	Phe	Arq	Met	Thr	Leu	Leu	Thr	_	Glv	Glv	Ala	Gly		Leu
			180					185		•	•		190		
Tyr	Val	Arg	Trp	Arg	Ile	Met	Gly	Thr	Gly	Pro	Pro	Ala	Phe	Thr	Glu
-		195	-	-			200		-			205			
Val	Asp	Asn	Pro	Ala	Ser	Phe	Ala	Asp	Ser	Met	Leu	Val	Arg	Ala	Val
	210					215		-			220				
Asn	Тут	Asn	Tyr	Tyr	Tyr	Ser	Leu	Asn	Ala	Trp	Leu	Leu	Leu	Cys	Pro
225					230					235					240
Trp	Trp	Leu	Суз	Phe	ĄzĄ	Trp	Ser	Met	Gly	Cys	Ile	Pro	Leu	Ile	Lys

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					245					250					255	
S	er	Ile	Ser	Asp	Trp	Arg	Val	Ile	Ala	Leu	Ala	Ala	Leu	Trp	Phe	Cys
				260					265					270		
L	eu	Ile	Gly	Leu	Ile	Суз	Gln	Ala	Leu	Cys	Ser	Glu	Asp	Gly	His	Lys
			275					280					285			
A	rg	Arg	Ile	Leu	Thr	Leu	Gly	Leu	Gly	Phe	Leu	Val	Ile	Pro	Phe	Leu
		290					295					300				
P	ro	Ala	Ser	Asn	Leu	Phe	Phe	Arg	Val	Gly	Phe	Val	Val	Ala	Glu	Arg
3	05					310					315					320
V	al	Leu	Tyr	Leu	Pro	Ser	Ile	Gly	Tyr	Cys	Val	Leu	Leu	Thr	Phe	Gly
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P	he	Gly	Ala	Leu	Ser	Lys	His	Thr	Lys	Lys	Lys	Lys	Leu	Ile	Ala	Ala
				340					345					350		
V	al	Val	Leu	Gly	Ile	Leu	Phe	Ile	Asn	Thr	Leu	Arg	Cys	Val	Leu	Arg
			355					360					365			
S	er	Gly	Glu	Trp	Arg	Ser	Glu	Glu	Gln	Leu	Phe	Arg	Ser	Ala	Leu	Ser
		370					375					380				
V	al	Суз	Pro	Leu	Asn	Ala	Lys	Val	His	Tyr	Asn	Ile	Gly	Lys	Asn	Leu
3	85					390					395					400
A	la	Asp	Lys	Gly	Asn	Gln	Thr	Ala	Ala	Ile	Arg	Tyr	Tyr	Arg	Glu	Ala
					405					410					415	
V	al	Arg	Leu	Asn	Pro	Lys	Tyr	Val	His	Ala	Met	Asn	Asn	Leu	Gly	Asn
				420					425					430	٠	
I	le	Leu	Lys	Glu	Arg	Asn	Glu	Leu	Gln	Glu	Ala	Glu	Glu	Leu	Leu	Ser
			435					440					445			
L	eu	Ala	Val	Gln	Ile	Gln	Pro	Asp	Phe	Ala	Ala	Ala	Trp	Met	Asn	Leu
		450					455					460				
G	ly	Ile	Val	Gln	Asn	Ser	Leu	Lys	Arg	Phe	Glu	Ala	Ala	Glu	Gln	
	65					470					475					480
T	уr	Arg	Thr	Ala	Ile	Lys	His	Arg	Arg	Lys	Tyr	Pro	Asp	Cys	Tyr	Tyr
					485					490					495	
A	sn	Leu	Gly	Arg	Leu	Tyr	Ala	Asp	Leu	Asn	Arg	His	Val	Asp	Ala	Leu
				500					505					510		
A	sn	Ala	Trp	Arg	Asn	Ala	Thr	Val	Leu	Lys	Pro	Glu	His	Ser	Leu	Ala
			515					520					525			

80

## 115/233

Trp			n Met	: Ile	∍ Ile	Leu	Leu	Asp	Asn	Thr	Gly	Asn	Leu	Ala	Gln
	530					535			,		540				
Ala	Glu	Alε	val	. Gly	Arg	Glu	Ala	Leu	Glu	Leu	Ile	Pro	Asn	Asp	His
545					550					555					560
Ser	Leu	Met	Phe	Ser	Leu	Ala	Asn	Val	Leu	Gly	Lys	Ser	Gln	Lys	Tyr
				565					570				•	575	
Lys	Glu	Ser	Glu	Ala	Leu	Phe	Leu	Lys	Ala	Ile	Lys	Ala	Asn	Pro	Asn
			580	ı				585					590		
Ala	Ala	Ser	Tyr	His	Gly	Asn	Leu	Ala	Val	Leu	Tyr	His	Arg	Trp	Gly
		595					600					605			
His	Leu	Asp	Leu	Ala	Lys	Lys	His	Tyr	Glu	Ile	Ser	Leu	Gln	Leu	Asp
	610					615					620				
Pro	Thr	Ala	Ser	Gly	Thr	Lys	Glu	Asn	Tyr	Gly	Leu	Leu	Arg	Arg	Lys
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Leu	Glu	Leu	Met	Gln	Lys	Lys	Ala	Val							
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1				5					10					15	
Ala	Ala	Gln	Thr	Thr	Pro	Gly	Glu	Arg	Ser	Ser	Leu	Pro .	Ala	Phe	Tyr
			20					25					30		
Pro	Gly	Thr	Ser	Gly	Ser	Cys	Ser	Gly	Cys	Gly .	Ser :	Leu :	Ser :	Leu :	Pro
		35					40					45			
Leu	Leu .	Ala	Gly	Leu	Val .	Ala .	Ala	Asp .	Ala '	Val 1	Ala :	Ser 1	Leu :	Leu :	Ile
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Val	Gly A	Ala	Val	Phe	Leu	Cys .	Ala .	Arg I	Pro J	Arg I	Arg 8	Ser 1	ero i	Ala (	3ln

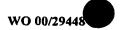
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Val	Val	Lys	Glu	Leu	Pro	Glu	Gly	Trp	Ser	Leu	Pro	Ser	Tyr	Val	Ser
			20					25					30		
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Arg	Arg	Leu	Ala	Pro	Gly	Lys	Asp	Glu	Gln	Val	Pro	Ile	Arg	Val	Val
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Gln	Val	Leu	Gly	Met	Val	Gly	Thr	Ala	Leu	Leu	Ala	Ser	Leu	Trp	His
65					70					75					80
His	Val	Ala	Pro	Val	Ala	Gly	Gln	Leu	His	Ser	Val	Ala	Phe	Leu	Ala
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Leu	Ala	Phe	Val	Leu	Ala	Leu	Ala	Cys	Cys	Ala	Ser	Asn	Val	Thr	Phe
			100					105					110		
Leu	Pro	Phe	Leu	Ser	Hìs	Leu	Pro	Pro	Arg	Phe	Leu	Arg	Ser	Phe	Phe
		115					120					125			
Leu	Gly	Gln	Gly	Leu	Ser	Ala	Leu	Leu	Pro	Суз	Val	Leu	Ala	Leu	Val
	130					135					140				
Gln	Gly	Val	Gly	Arg	Leu	Glu	Суз	Pro	Pro	Ala	Pro	Ile	Asn	Gly	Thr
145					150					155					160
Pro	Gly	Pro	Pro	Leu	Asp	Phe	Leu	Glu	Arg	Phe	Pro	Ala	Ser	Thr	Phe
				165					170					175	
Phe	Trp	Ala	Leu	Thr	Ala	Leu	Leu	Val	Ala	Ser	Ala	Ala	Ala	Phe	Gln
			180					185					190		
Gly	Leu	Leu	Leu	Leu	Leu	Pro	Pro	Pro	Pro	Ser	Val	Pro	Thr	Gly	Glu
		195					200					205			
Leu	Gly	Ser	Gly	Leu	Gln	Val	Gly	Ala	Pro	Gly	Ala	Glu	Glu	Glu	Val
	210					215					220				
Glu	Glu	Ser	Ser	Pro	Leu	Gln	Glu	Pro	Pro	Ser	Gln	Ala	Ala	Gly	Thr
225					230					235					240



1111	FIO	GLY	FIU	nsp	FLO	цу	, MTG	тут	. GII	1 Let	L	i sei	. AIC	rwr	y se
				245					250	0				255	5
Ala	Cys	Leu	Leu	Gly	Leu	Leu	Ala	Ala	Thi	Asn	Ala	Let	Thr	: Ası	n Gly
			260					265	•				270	)	
Val	Leu	Pro	Ala	Val	Gln	Ser	Phe	Ser	Cys	. Leu	Pro	Туг	Gly	' Arg	j Lei
		275					280					285	•		
Ala	Tyr	His	Leu	Ala	Val	Val	Leu	Gly	Ser	Ala	Ala	Asn	Pro	Leu	a Ala
	290					295					300				
Cys	Phe	Leu	Ala	Met	Gly	Val	Leu	Cys	Arg	, Ser	Leu	Ala	Gly	Lev	ı Gly
305					310					315					320
Gly	Leu	Ser	Leu	Leu	Gly	Val	Phe	Cys	Gly	Gly	Tyr	Leu	Met	Ala	Leu
				325					330	)				335	,
Ala	Val	Leu	Ser	Pro	Cys	Pro	Pro	Leu	Val	Gly	Thr	Ser	Ala	Gly	Val
			340					345					350		
Val	Leu	Val	Val	Leu	Ser	Trp	Val	Leu	Cys	Leu	Gly	Val	Phe	Ser	Туг
		355					360					365			
Val	Lys	Val	Ala	Ala	Ser	Ser	Leu	Leu	His	Gly	Gly	Gly	Arg	Pro	Ala
	370					375					380				
Leu	Leu	Ala	Ala	Gly	Val	Ala	Ile	Gln	Val	Gly	Ser	Leu	Leu	Gly	Ala
385					390					395					400
Val	Ala	Met	Phe	Pro	Pro	Thr	Ser	Ile	Tyr	His	Val	Phe	His	Ser	Arg
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Lys	Asp	Суз	Ala	Asp	Pro	Суз	Asp	Ser							
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Leu Lys Leu Lys Lys Pro Pro Trp Leu His Met Pro Ser Ala Met Thr

Val Tyr Ala Leu Val Val Val Ser Tyr Phe Leu Ile Thr Gly Gly Ile

25

20

35	40	45
Ile Tyr Asp Val Ile Val	Glu Pro Pro Ser	Val Gly Ser Met Thr Asp
50	55	60
Glu His Gly His Gln Arg	Pro Val Ala Phe	Leu Ala Tyr Arg Val Asn
65 70	)	75 80
Gly Gln Tyr Ile Met Glu	Gly Leu Ala Ser	Ser Phe Leu Phe Thr Met
85	90	95
Gly Gly Leu Gly Phe Ile	e Ile Leu Asp Arg	Ser Asn Ala Pro Asn Ile
100	105	110
Pro Lys Leu Asn Arg Phe	Leu Leu Leu Phe	Ile Gly Phe Val Cys Val
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Val Leu Leu Phe Cys Glu		Tyr Leu Ala Ile Phe Gln
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		Ser Asp Gly Glu Gln Thr
50	55	60
-		Leu Ala Asp Thr His Leu
65 70		75 80
_		Lys Leu Arg Arg Glu Trp
85	90	95
		Trp Leu Leu Gln Pro Glu 110
100	105	

Val	L Vai	l Ph	e Il	e Le	u Gly	/ As	p Ile	e Ph	e As	p Gl	u Gl	у Lу	s Tr	p Se	r Thr
		11	5				120	)				12	5		
Pro	Gli	ı Al	a Tr	p Al	a Ası	) Asj	p Val	l Gl	u Ar	g Ph	e Gl	n Ly	s Met	t Ph	e Arg
	130	)				13	5				140	)			
His	Pro	Se	r Hi	s Va	l Glr	Le	ı Lys	Va.	l Va	l Al	a Gly	/ Asi	n His	a As	p Ile
145	i				150	)				15	5				160
Gly	Phe	Hi:	s Ty	r Gl	u Met	Ası	ı Thr	Туз	Ly	s Vai	l Glu	ı Arç	J Phe	e Gl	ı Lys
				16	5				170	0				175	5
Val	Phe	Se	r Se	r Gl	ı Arg	Let	. Phe	Ser	Tij	p Lys	s Gly	, Ile	a Asr	ı Phe	e Val
			180	0				185	; ·				190	)	
Met	Val	Ası	ı Sei	r Val	l Ala	Let	Asn	Gly	As <sub>I</sub>	o Gly	7 Cys	Gly	' Ile	: Cys	s Ser
		195	5				200	)				205	;		
Glu	Thr	Glu	a Ala	a Glu	ı Leu	Ile	Glu	Val	Ser	His	Arg	Leu	Asn	Cys	Ser
	210	ı				215	į				220				
Arg	Glu	Ala	Arg	g Gly	ser	Ser	Arg	Cys	Gly	Pro	Gly	Pro	Leu	Leu	Pro
225					230					235					240
Thr	Ser	Ala	Pro	Val	. Leu	Leu	Gln	His	Туг	Pro	Leu	Tyr	Arg	Arg	Ser
				245	i				250	)				255	
Asp	Ala	Asn	Cys	Ser	Gly	Glu	Asp	Ala	Ala	Pro	Ala	Glu	Glu	Arg	Asp
			260	)				265					270		
Ile	Pro	Phe	Lys	Glu	Asn	Tyr	Asp	Val	Leu	Ser	Arg	Glu	Ala	Ser	Gln
		275					280					285			
Lys	Leu	Leu	Trp	Trp	Leu	Gln	Pro	Arg	Leu	Val	Leu	Ser	Gly	His	Thr
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305					310					315					320
Val	Pro	Ser	Phe	Ser	Trp	Arg	Asn	Arg	Asn	Asn	Pro	Ser	Phe	Ile	Met
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Gly	Ser	Ile	Thr	Pro	Thr	Asp	Tyr	Thr	Leu	Ser	Lys	Cys	Tyr	Leu	Pro
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Arg			Val	Val	Leu	Ile	Ile	Tyr	Cys	Gly	Val	Val	Gly	Phe	Leu
		355					360					365			
		Leu	Thr	Leu	Thr		Phe	Gly	Leu	Leu	Ala	Ser	Pro	Phe	Leu
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Glu Thr Val Arg Val	Gln Gly Pro Gly	Ile Leu Pro Gly 1	Leu Asp Ser
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Glu Ser Ala Ser Ser	Ser Ile Arg Phe S	Ser Lys Ala Cys I	Leu Lys Asn
50	55	60	
Val Phe Ser Val Leu	Leu Ile Phe Ile 7	Tyr Leu Leu Leu M	Met Ala Val
65	70	75	80
Ala Val Phe Leu Val	Tyr Arg Thr Ile 1	Thr Asp Phe Arg (	
85		90	95
Lys His Pro Val Met	Ser Val Ser Tyr I		
100	105	•	110
Ala Pro Gly Ile Ala			Leu Ser Cys
115	120	125	
Lys His His Tyr Glu			Ely Gin Pro
130	135	140	
Gly Asp Met Asn Cys			
145	150	155	160
Ser Asn Gln Thr Val			175
165		170	
Val Lys Lys Arg Glu			ish hys ser
180	185		
Ser Glu Asp Phe Ser 195	200	Leu Leu File Sei S 205	CL EIN GIH
Glu Phe Leu Gln Ser			da Cvs Glu
	215	220	
210	213	220	

Ser	Ala	Tyr	Ser	Ser	Trp	Lys	Phe	Ser	Gly	Gly	Phe	Arg	Thr	Trp	Val
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Lys	Met	Ser	Leu	Val	Lys	Thr	Lys	Glu	Glu	Asp	Gly	Arg	Glu	Ala	Val
				245					250					255	
Glu	Phe	Arg	Gln	Glu	Thr	Ser	Val	Val	Asn	Tyr	Ile	Asp	Gln	Arg	Pro
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Ala	Ala	Lys	Lys	Ser	Ala	Gln	Leu	Phe	Phe	Val	Val	Phe	Glu	Trp	Lys
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	290					295					300				
Asn	Thr	Ile	Ala	Leu	Leu	Cys	Gly	Ala	Phe	Leu	Ala	Leu	Phe	Lys	Ala
305					310					315					320
Ala	Glu	Phe	Ala	Lys	Leu	Ser	Ile	Lys	Trp	Met	Ile	Lys	Ile	Arg	Lys
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<212> PRT

<213> Homo sapiens

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Gln His Arg Gly His Val Cys Tyr Leu Gly Val Cys Arg Thr His Arg

35 40 45

Leu Ala Glu Ile Ile Tyr Trp Ile Arg Cys Leu His Gln Gly Ala Leu
50 55 60

Gly Glu Gly Gln Pro Arg Ala Pro Gly Pro Leu Gln Leu Trp Ala Pro 65 70 75 80

Pro Val Ala Arg Gly Gly Ser Pro Ala Arg Phe Pro Gly Phe Arg Pro 85 90 95

Ala Ala Arg Gly Leu Ala Gln Cys Pro Ala Arg Trp Val Thr Ser Gly

110 105 100 Thr Ala Arg Pro Leu Leu Gly Phe Ser Leu Pro Ile Cys Met Leu Glu 125 120 115 Leu Leu Leu His Ile Ser Ser Pro Leu Thr Pro Ala Pro Glu Thr Val 140 135 Phe Pro Ser Pro Ser Pro Gly Cys Asp 150 145 <210> 71 <211> 1176 <212> DNA <213> Homo sapiens <400> 71 60 atggagggag tgagegeget getggeeege tgeeecaegg eeggeetgge eggeggeetg ggggtcacgg cgtgcgccgc ggccggcgtg ttgctctacc ggatcgcgcg gaggatgaag 120 180 ccaacgcaca cgatggtcaa ctgctggttc tgcaaccagg atacgctggt gccctatggg 240 aacegcaact gctgggactg tccccactgc gagcagtaca acggcttcca ggagaacggc 300 gactacaaca agccgatccc cgcccagtac ttggagcacc tgaaccacgt ggtgagcagc 360 gegeceagee tgegegaeee ttegeageeg cageagtggg tgageageea agteetgetg tgcaagaggt gcaaccacca ccagaccacc aagatcaagc agctggccgc cttcgctccc 420 480 cgcgaggagg gcaggtatga cgaggaggtc gaggtgtacc ggcatcacct ggagcagatg tacaagetgt geeggeegtg ecaagegget gtggagtaet acateaagea eeagaacege 540 600 cagctgcgcg ccctgttgct cagccaccag ttcaagcgcc gggaggccga ccagacccac gcacagaact tetecteege egtgaagtee eeggteeagg teateetget eegtgeeete 660 720 gcettectgg cetgegeett cetactgace accgegetgt atggggccag eggacactte 780 gececaggea ceaetgtgee eetggeeetg eeaeetggtg geaatggete agecaeaeet 840 gacaatggca ccaccctgg ggccgaggcc tggcggcagt tgctgggcct actccccgag 900 cacatggcgg agaagctgtg tgaggcctgg gcctttgggc agagccacca gacgggcgtc 960 gtggcactgg gcctactcac ctgcctgctg gcaatgctgc tggctggccg catcaggctc 1020 eggaggateg atgeettetg eacetgeetg tgggeeetge tgetgggget geacetgget 1080 · gagcagcacc tgcaggccgc ctcgcctagc tggctagaca cgctcaagtt cagcaccaca 1140 tetttgtget geetggttgg etteaeggeg getgtggeea caaggaagge aaegggeeea

1176

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WO 00/29448 PCT/JP99/06412

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<400> 73

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360

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480

#### 124/233

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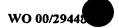
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240



### 125/233

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<400> 77

1188



### 127/233

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Can <td>Call Ring Ring Part 1         See See Sign Wat 1         Lew Lieu Cys Ring Ring Name 1         Lew Ring Ring Ring Name 1         Lew Ring Ring Ring Ring Ring Ring Ring Ring</td> <td>Call Rin Rin Rin Rin Rin Rin Rin Rin Rin Rin</td> <td>Cac cag ac cag ac ag ac ag ctg gag gag gt cac ag ctg gcg gcc tc gcc ccc ccc  His Gln Thr Thr Lys Ile Lys Gln Leu Ala Ala Phe Ala Pro Arg  130 135 140  gag ggc agg tat gac gag gag gtc gag gtg tac cgg cat cac ctg Glu Gly Arg Tyr Asp Glu Glu Val Glu Val Tyr Arg His His Leu  145 150 155 155  cag atg tac aag ctg tgc cgg cgg tgc tac ag gcg gtg gag tac Gln Met Tyr Lys Leu Cys Arg Pro Cys Gln Ala Ala Val Glu Tyr  160 165 170  atc aag cac cag aac cgc cag cag ctg cgc ctg tgc cac agc Ile Lys His Gln Asn Arg Gln Leu Arg Ala Leu Leu Ser His  175 180 185  ttc aag cgc cgg gag gcc gac gac ac cag acc cag acc cag Ala Val Lys Ser Pro Val Gln Val Ile Leu Leu Arg Ala Leu Leu Ser  Ala Val Lys Ser Pro Val Gln Val Ile Leu Leu Arg Ala Leu Leu Ser  Leu Ala Cys Ala Phe Leu Leu Thr Thr Ala Leu Tyr Gly Ala Ser  225 230 235  cac ttc gcc cca ggc acc acc acc acc acc acc ac</td>	Call Ring Ring Part 1         See See Sign Wat 1         Lew Lieu Cys Ring Ring Name 1         Lew Ring Ring Ring Name 1         Lew Ring Ring Ring Ring Ring Ring Ring Ring	Call Rin	Cac cag ac cag ac ag ac ag ctg gag gag gt cac ag ctg gcg gcc tc gcc ccc ccc  His Gln Thr Thr Lys Ile Lys Gln Leu Ala Ala Phe Ala Pro Arg  130 135 140  gag ggc agg tat gac gag gag gtc gag gtg tac cgg cat cac ctg Glu Gly Arg Tyr Asp Glu Glu Val Glu Val Tyr Arg His His Leu  145 150 155 155  cag atg tac aag ctg tgc cgg cgg tgc tac ag gcg gtg gag tac Gln Met Tyr Lys Leu Cys Arg Pro Cys Gln Ala Ala Val Glu Tyr  160 165 170  atc aag cac cag aac cgc cag cag ctg cgc ctg tgc cac agc Ile Lys His Gln Asn Arg Gln Leu Arg Ala Leu Leu Ser His  175 180 185  ttc aag cgc cgg gag gcc gac gac ac cag acc cag acc cag Ala Val Lys Ser Pro Val Gln Val Ile Leu Leu Arg Ala Leu Leu Ser  Ala Val Lys Ser Pro Val Gln Val Ile Leu Leu Arg 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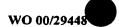
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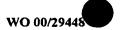
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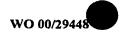
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Ala Asn Ser As	sp Leu Lys Val	Leu Leu Cys	Gly Pro Val	Gly Pro Arg	Ī
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Leu His Glu Le	eu Leu Asp Asp	Asn Val Phe	Val Pro Pro	Glu Ser Leu	ı
185	190		195	200	)
cag gaa gtg ga	at gag ttc cac	ctc att tta	gag tat caa	gca ggg gag	677
Gln Glu Val As	sp Glu Phe His	Leu Ile Leu	Glu Tyr Gln	Ala Gly Glu	l .
•	205	210		215	
gag tgg ggc ca	ng tta aaa gct	ccc cat gcc	aac cga ttc	atc ttc tct	725
Glu Trp Gly Gl	ln Leu Lys Ala	Pro His Ala	Asn Arg Phe	Ile Phe Ser	•
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His Asp Leu Se	er Asn Gly Ala	Met Asn Met	Leu Glu Val	Phe Val Ser	•
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Ser Leu Glu Gl	u Phe Gln Pro	Asp Leu Val	Val Leu Ser	Gly Leu His	i
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Met Met Glu Gl	y Gln Ser Lys	Glu Leu Gln	Arg Lys Arg		
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gtt gta acc to					
Val Val Thr Se	er Ile Ser Asp	Ile Pro Thr	Gly Ile Pro	Val His Leu	!
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Glu Leu Ala Se	er Met Thr Asn	Arg Glu Leu	Met Ser Ser		
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cag cag gtc tt					
Gln Gln Val Ph	ne Pro Ala Val	Thr Ser Leu		Glu Gln Glu	
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ctg tta ttt ct					
Leu Leu Phe Le	eu Thr Gln Ser	Ala Ser Gly		Ser Leu Ser	•
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tee tgg aac gg	ft gtt cct gat	gtg ggc atg	gtc agt gac	ate ete tte	1109



ser	Trp	Asn	GTĀ	vai	Pro	Asp	Val	GTĀ	Met	Val	Ser	Asp	He	Leu	Phe	
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Thr	Arg	Ile	His	Phe	His	Thr	Leu	Val	Tyr	His	Ile	Leu	Ala	Thr	Val	
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Asp	Gly	His	Trp	Ala	Asn	Gln	Leu	Ala	Ala	Val	Ala	Ala	Gly	Ala	Arg	
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Pro	Ile	Arg	Thr	Val	Gly	Leu	Gly	Asp	Ala	Ile	Ser .	Ala	Glu	Gly	Leu	
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tc 1	tat	tcg	gaa	gta	cac	cct	cac	tat	tagg	aaga	tt c	ttag	gggt	a		1540
?he !	Tyr	Ser	Glu '	Val	His	Pro	His	Tyr								
4	490					495										
attti	ttct	ga g	gaag	gaga	a ct	agcc	aact	taa	gaat	tac	agga	agaa	ag t	ggtti	tggaa	1600
jaca	gcca	aa g	aaat	aaaa	g ca	gatt	aaac	tgt	atca	ggt	acat	tcca	ge et	tgtt	ggcaa	1660
tec	ataa	aa a	catt	tcag	a tt	ttaa	teeg	aat	ttag	cta :	atga	gact	gg at	tttt	tgttt	1720
ttat	tgtt	gt gi	tgtc	acag	a gc	taaa	aact	cag	ttcc	caa (	atcc	ccagt	tt ta	atge	agege	1780
atca	aggt	at ti	ttaa	gcta	a ac	ttct	tcac	ccc	tgag	agc a	atgto	cagct	eg ga	agaaa	aagca	1840
++~+	+~~	tt ac	2002	n++~:	- 42	o at a	7200	000	ooto:			+~~	-~ ~			1000

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Leu	Cys	Glu	ı Ala	a Glu	ı Glu	ı Ala	Pro	Pro	Ala	Ser	Ser	Thr	Pro	His	val	
95	i				100	)				105	•				110	
gtg	ggg	tct	: cgc	: ttt	aac	tgg	aag	ctc	tto	tgg	cag	, ttt	cto	cad	ccc	444
Val	Gly	Ser	Arg	Phe	e Asn	Trp	Lys	Leu	Phe	Trp	Gln	Phe	Lev	His	Pro	
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cac	ctg	ctg	gto	cto	<b>a</b>	gta	gcc	gtc	gtg	ctg	gcc	ttg	ggt	gcg	gca	492
His	Leu	Leu	\ Val	. Let	Gly	Val	Ala	Val	Val	Leu	Ala	Leu	Gly	Ala	Ala	
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															gte	540
Leu	Val			Gln	Ile	Pro			Leu	Gly	Gln			Glu	Val	
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										agt		_				588
VAI	160		туг	unr	Arg	_	HIS	Val	GIĀ	Ser			Thr	GIU	Ser	
<b>CP</b> C			9.00	B.C.C	020	165	<b></b>	a <b>t</b> -	-+-		170					£2£
			_			_				tat Tyr		_	_		_	636
175	110.1		501	1111	180	neu	Leu	116	Leu	185	GIY	Val	GIII	GLY	190	
	acc	tte	aaa	tac		ata	cta	cta	tcc	cac	att	aac	gag	cac		684
										His						001
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Phe	T.vs	Ser	Ser	Phe	Lvs	Leu	Val	Tle	Ser	Gln	Glv	Ten	Δτα	Sar	Cve	

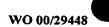
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Gln	Arg	Leu														
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Asp Phe Val Phe Asp Asp Ser Glu Ala Ile Val Asn Asn Lys Val Al	
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Pro	Ala	Phe	Thr	Glu	Val	Asp	Asn	Pro	Ala	Ser	Phe	Ala	Asp	Ser	Met	
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Leu	Val	Arg	Ala	Val	Asn	Tyr	Asn	Tyr	Tyr	Tyr	Ser	Leu	Asn	Ala	Trp	
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Ile	Pro	Leu	Ile	ГÀЗ	Ser	Ile	Ser	ĄzĄ	Trp	Arg	Val	Ile	Ala	Leu	Ala	
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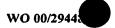
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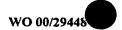
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	GIU	ser	ser	PIO		GIN	GIU	Pro	Pro		GIN	Ala	Ala	СТА		
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Val	Leu	Val	Val	Leu	Ser	Trp	Val	Leu	Cys	Leu	Gly	Val	Phe	Ser	Tyr	
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Glu	Thr	Leu	Тух	Arg	Val	Pro	Phe	Leu	Val	Leu	Glu	Суз	Pro	Asn	Leu		
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Gln !	Tyr	Ile	Met	Glu	Gly	Leu	Ala	Ser	Ser	Phe	Leu	Phe	Thr	Met	Gly		
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3ly 1	Leu	Gly	Phe	Ile	Ile	Leu	qzA	Arg	Ser	Asn	Ala	Pro	neA	Ile	Pro		
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Mot Ala Val Ala Val Dha Yau Val Dama Ann mha ala mha ann at	
Met Ala Val Ala Val Phe Leu Val Tyr Arg Thr Ile Thr Asp Phe Arg	

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Ser	
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780

783

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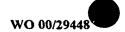
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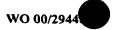
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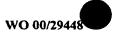


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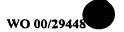
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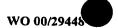
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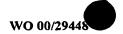
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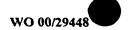
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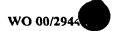
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cay c Gln A																		
сіп А	μg	AGT	var	AL 9	FIU	ıı <del>c</del> u.	LIE	TIGIT	ALY.	いてつ		J-X	2244	A CIT	-	'E'		



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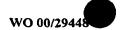


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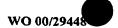
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Asp Asn Ile Arg Glu Phe Leu Leu Ser Leu Arg Tyr Phe Arg Ile Phe	
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Arg Glu Arg Gly Glu Leu Leu Val His Thr Gly Phe Leu Gly Ser	
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Ser Gln Asp Arg Ser Ala Tyr Gln Thr Ile Asp Ser Ala Glu Ala Pro	
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Ala Asp Pro Phe Ala Val Pro Glu Gly Arg Ser Gln Asp Ala Arg Gly	
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Ser Thr Leu Val Pro Leu Arg Leu Arg His Arg Gln Leu Gly Leu Gln	
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Ala	Lys	Gly	Trp	) Asr	Phe	Met	Let	ı Glı	ı Ası	Se:	r Thi	r Ph	e Tr	p Il	e Ph
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Gly	Gly	Ser	Ile	His	Tyr	Phe	Arç	y Val	l Pro	Arq	g Glı	тут	r Tr	p Ar	g As
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Arg	Leu	Leu	Lys	Met	Lys	Ala	Cys	Gl	Let	ı Ası	1 Thi	: Le	ı Thi	r Thi	г Ту
				85					90	)				9:	5
Val	Pro	Trp	Asn	Leu	His	G1u	Pro	Glu	a Arg	g Gly	Lys	Phe	a Asp	Phe	e Sei
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Gly	Asn	Leu	Asp	Leu	Glu	Ala	Phe	Val	. Leu	Met	Ala	Ala	a Glu	ı Ile	e Gly
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Leu	Trp	Val	Ile	Leu	Arg	Pro	Gly	Pro	Tyr	Ile	Cys	Ser	Glu	ı Met	e Asp
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Pro	Cys	Asp	Thr	Phe	Leu	Lys	Leu	Glu	Gly	Trp	Glu	Lys	Gly	Val	Val
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Lys	Thr	Leu	Tyr	Leu	Pro	Gly	Pro	Trp	Leu	Ser	Ser	Gly	Ile	Asn	Gln
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Lys Ser Gln Leu Met Asn Leu Ile Arg Ser Val Arg Thr Val Met Arg
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Lys	Glu	Leu	Asp	Lys	Gly	Val	Gln	Gly	Leu	Asn	His	Gly	Met	Asp	Lys
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Glu		Asp	Lys	Ala	Val		Gly	Phe	His	Thr	_	Val	His	Gln	Ala
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Gln	Ala	GIĀ	Lys		Val	Glu	Lys	Leu		Gln	GLY	Ala	His		ALE
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ALA	GIĀ	GIN		GIĀ	Lys	Glu	Leu		Asn	Ala	His	Asn		Vai	Asn
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_		Ser	ser	HIS	GIN	_	GIĀ	Ala	Thr	Thr		Pro	Leu	АТа	ser
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_	ATG	ser	vaT	ASN		r I O	LUE	тте	ASN	Leu	7.LO	₩TØ	reg	_	_
225	**- 7	<b>57</b> -	<b>N</b>	<b>~</b> 1 -	230	<b>n</b>				235					240
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Pro Le	u Val	Leu	Glu	Met	Leu	Lys	Ala	Gly	Val	Lys	Asp	Thr	Glu	Ası
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Val	Leu	Ala	Leu	Ile	Val	Ala	Gly	Leu	Ser	Cys	Val	Leu	Cys	Lys	Glı
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Pro	Arg	His	Gly	Ala	Pro	Met	Tyr	Arg	Tyr	Ser	Phe	Ala		Leu	Sea
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Gln	Gly	Ala	Leu	Leu	Glu	Gly	Thr	Arg	Phe	Met	Gly	Arg	His	Ser	Glu
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45

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Ara .	Asn	Ara	Tle		Asn	Agn	Pro	ĄsĄ		Dro	Glu	Δla	ጥኮ፦		Ara	
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Leu :	Lvs	Leu		Met	Ile	Gln	Gln	Tyr	T.e.11	Lvs	Val			Cvs	Glu	
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Trp Leu Tyr Arg Ala Ile Leu Ser Leu Tyr Ile Leu Leu Ala Leu Ala
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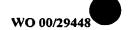
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#### 204/233

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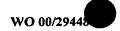
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<221> CDS

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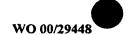
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Ala Ile Val Leu Leu Leu Phe Gly	
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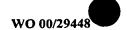
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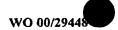
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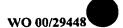
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ASN	vaı	195	ser	ser	Trp	Cys	Gln	TYL	GIU	ALA	Leu	டர் 205	Pne	vaı	ser	
++0	000		<b>C2C</b>	a+ a	ot a	~~~	200	~~~	tat	224	at a		cot	at a	sta	789
			_		_	_	aag Lys	_		_				_		,09
	210	1111	GIII	val	Dea	215	пЛэ	ATG	Ser	Бур	220	TTG	PIO	var	ricc	
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	aca	acc	aca	ete		tee	att	aaa	ata		ata	ttt	cta	cta		885
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Arg	Lys	Tyr	Tyr	Ser	Thr	Thr	His	Gly	Ala	Leu	Leu	Ser	Gly	Gln	Arg	
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gag	gat	gee	cgc	ctc	att	gag	atg	tac	cga	gac	ctc	ttc	cag	cag	ggg	1865
Glu	Ala	Ala	Arg	Leu	Ile	Glu	Met	Tyr	Arg	qaA	Leu	Phe	Gln	Gln	Gly	
	540					545					550					
acc	tgag	Jggct	gt c	ctc	getge	t ga	ıgaaç	gagco	act	aact	cgt	gaco	tcca	ige c	:t	1920
Thr																
555																
geed	ctto	jet <u>c</u>	geegt	gtgo	et co	tgec	ttcc	tga	atcct	ctg	taga	aagg	rat t	ttta	tette	1980
tgte	gago	ta ç	jeege	cct	ja ct	gcct	tcag	g acc	tggc	cct	gtag	jcttt	tc t	tttt	ctcca	2040
ggct	gggc	eg t	gago	aggt	g gg	ccgt	tgag	; tta	ecto	tgt	geto	gato	cc g	rtgcc	cccac	2100
ttgc	ctac	ecc t	ctgt	cct	je et	tgtt	atto	, tas	gtgo	ctt	caat	actt	tg c	attt	tggga	2160
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														r Ala		
								1	L			!	5			
gat ga	t ego	ccc	te	tec	t tg	agg	g cga	aag	g caa	a gae	a gat	gad	e ag	g gac	1	161
Ala Ala	a Arç	Pro	Sea	. Sei	Cys	Arg	, Arg	Lys	Glı	n Glu	ı Ası	As <sub>l</sub>	o Ar	g Asp		
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Gly Le	ı Leu	Ala	Glu	ı Arg	Glu	Gln	Glu	Glu	Ala	a Ile	Ala	Glr	n Phe	Pro		
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Tyr Val	Glu	Phe	Thr	Gly	Arg	Asp	Ser	Ile	Thr	Cys	Leu	Thr	Cys	Gln		
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Ile Pro	His	Ser	Asp	Gln	Arg	Leu	Arg	Pro	Gln	Arg	Thr	Lys	Gln	Tyr		
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gte ete													-		40	01
Val Leu	Leu	Ser	Ile	Leu	Leu	Cys	Leu	Leu	Ala	Ser	Gly	Leu	Val	Val		
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Phe Phe	Leu	Phe	Pro	His	Ser	Val	Leu	Val	Asp	Asp	Asp	Gly	Ile	Lys		
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lle Met Ala Thr Leu Lys Ile Arg Asn Ser Asn Phe Tyr Thr Val Ala	
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Val Thr Ser Leu Ser Ser Gln Ile Gln Tyr Met Asn Thr Val Val Ser	
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Leu Val Asn Phe Thr Gly Lys Ala Glu Met Gly Gly Pro Phe Ser Tyr	
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Val Tyr Phe Phe Cys Thr Val Pro Glu Ile Leu Val His Asn Ile Val	
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Gln Ser Ser Leu Glu Thr His His Tyr Val Asp Cys Gly Gly Asn Ser	
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Thr Ala Ile	
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		Gly	Val	. Ser	Ala	Lys	Asn	Gln	Gly	Ala	His	Asp	Pro	Asp	Tyr	
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Glu	Asn	Ile	Thr			Phe	Lys	Asn		_	His	Ala	Lys		Gly	
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HIS	Ser	Arg			Ser	Gln	Val	Pro	Ala	Gln	Суз	Arg		Pro	Ser	
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nap	Ser	60		val	PIO	Cys		Leu	TYL	Arg	Ald	70	ren	Ser	Leu	
tec	ato			<i>~~</i>	a+a	<i>~~~</i>	65	-+-	ata	+~~	et a		at a	tas	gaa	292
				_	_	_		gtc Val		_			_			292
-1-	75		204		Lou	80	F 11C	VUL		Cys	85	116	cu	DOL	ща	
ttc		ato	at.a	aac	eat.	-	gag	atg	tee	aaα		cta	cta	aac	ttt	340
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_	_			110					115				-	120		
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Arg Ser Lys Ile Asp Ar	g Leu Glu Thr Thr Leu	Ala Gly Ile Lys Asn	
140	145	150	,
att gac aca aag gta ca	ng ama atc ttg gag gtg	ctg cag aaa atg cca	532
Ile Asp Thr Lys Val Gl	n Lys Ile Leu Glu Val	Leu Gln Lys Met Pro	
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Gln Ser Ser Pro Gln			
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